Metal-Templated Assembly of Heterocyclic Rings via Nucleophilic Cyclization of Cyclopropenes

BY

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Metal-Templated Assembly of Heterocyclic Rings

via Nucleophilic Cyclization of Cyclopropenes

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Abstract

This thesis is focused on the development and application of methods for the intramolecular nucleophilic addition of tethered nucleophiles to cyclopropenes. Addition of carbon-, nitrogen, and oxygen-nucleophiles was demonstrated to provide access to γ-aminobutyric acid (GABA) derivatives and biologically relevant cyclopropane-fused heterocyclic rings (heteroazepanones, heteroazocanones, and pyrrolidinones). The thesis is divided into five chapters, which discuss not only the development and elaboration of our chemistry, but also biological importance and alternative methods for synthesis of target heterocycles presented in literature.

Chapter one is a review of biological activity, occurrence in nature, and synthetic approaches for the preparation of heteroazepanones and heteroazocanones. The chapter will describe methods based on cyclization and ring expansion reactions, as well as multicomponent and tandem methods.

Chapter two focuses on the one-pot synthesis of various γ-aminobutyric acid (GABA) amides through unassisted nucleophilic addition of primary and secondary amines across the double bond of cyclopropene-3-carboxamides. Initial nucleophilic attack is followed by a ring opening of the resulting donor-acceptor cyclopropanes. Subsequent in situ reduction of enamine or imine intermediates allows to access substituted GABA derivatives.

Chapter three describes a formal intramolecular nucleophilic substitution reaction of bromocyclopropanes with nitrogen ylides generated in situ from N-benzyl carboxamides. This reaction represents the 5-*exo-trig* cyclization through intermolecular base-assisted nucleophilic addition of tethered benzylic anion to cyclopropenes generated in situ by dehydrohalogenation of bromocyclopropanes.

Abstract (Continued)

Chapter four describes modular assembly of enantiopure cyclopropane-fused oxazepanones through a strain-release-driven, cation-templated intramolecular nucleophilic addition of tethered alkoxides to prochiral cyclopropenes. The mechanism of enantiomeric induction is detailed. The biological profile exhibited by some of obtained 2-oxa-5-azabicyclo[5.1.0]octan-6-ones is characterized by promising activity against *Mycobacterium abscessus* coupled with apparent low general toxicity against cultured human cells.

The final chapter covers ring-retentive 7- and 8-*exo-trig* nucleophilic attack of tethered nitrogen-based nucleophiles at cyclopropene double bond. The described potassium-templated cyclization proceeds in highly regio- and diastereoselective fashion and provides expedited access to previously unknown drug-like scaffolds including several structures with promising anti-cancer properties.

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Lastly, I would like to thank my friend Polina Boridko for encouragement and for always cheering me up.

I dedicate this thesis to Michael Rubin, my mentor and friend

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List of Schemes

Abbrevations

[H] or [red]	reduction
°C	degrees Celsius
µL	microliter
2D	two-dimensional
A	acceptor group
Å	angstrom
Ac	acetyl
ACC	aminocyclopropanecarboxylic acid
AcOH	acetic acid
ACS	American Chemical Society
Ad	adamantyl
AIBN	azobisisobutyronitrile
AIDS	acquired immunodeficiency syndrome
Alk	alkyl
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br.	broad
Bu	butyl
C	carbon
cat.	catalyst
Cbz	carboxybenzyl group
cm	centimeter
cod	1,5-cyclooctadiene
COSY	correlation spectroscopy
Cy	cyclohexyl
D	donor group
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DAC	donor–acceptor cyclopropanes
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine

DIPP	2,6-diisopropylphenyl
DMAP	4-(dimethylamino)pyridine
DMEM	Dulbecco's modified eagle medium
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
dt	doublet of triplets
E	electrophile
E. coli	escherichia coli
ED_{50}	median effective dose
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron donating group
equiv.	equivalent
ESI TOF	electrospray ionisation time-of-flight
Et	ethyl
et al.	and others
Et2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EtONa	sodium ethoxide
EWG	electron withdrawing group
FID	flame ionization detector
Fmoc	fluorenylmethyloxycarbonyl
FT IR	Fourier-transform infrared spectroscopy
g	gram
GABA	γ-aminobutyric acid
GC	gas chromatography
h or hr	hour
Hal	halogen
Het	heteryl
HIV	human immunodeficiency virus
HOBt	1-hydroxybenzotriazole
HRMS	high-resolution mass spectrometry
Hz	hertz
IC50	inhibitory concentration at 50%
i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant
kcal	Calorie (kilocalorie)

Ki	inhibitor constant
L	liter or ligand
LA	Lewis acid
LDA	lithium diisopropylamide
Li-CHIP	lithium cyclohexylisopropylamide
liq.	liquid
m	multiplet or meter
M	molarity or molecular ion
m-	meta-
Me	methyl
MeOH	methanol
MeONa	sodium methoxide
mg	milligram
MHz	megahertz
MIC	minimum inhibitory concentrations
min	minute
mL	milliliter
mm	millimeter
mmol	millimole
mol	mole
MTT	measuring cell metabolic activity
n-	normal-
NHC	*N*-heterocyclic Carbene
NIH	National Institute of Health
nm	nanometer
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o-	ortho-
p-	para-
PAO	phenyl arsine oxide
Pd/C	palladium on carbon
Ph	phenyl
ppm	parts per million
Pr	propyl
PTC	phase-transfer catalyst
R_f	retention factors
RSC	The Royal Society of Chemistry
RT or rt	room temperature
s	singlet
sat.	saturated

S_N	nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
t	triplet
t-	tert-
T3P	propylphosphonic anhydride
TBAF	tetra-*n*-butylammonium fluoride
TBHP	tert-butyl hydroperoxide
t-BuOK	potassium tert-butoxide
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF ES	electrospray ionisation time-of-flight
Ts	tosyl
TS	transition state

Chapter 1. Synthesis and biological importance of heteroazepanones and heteroazocanones

1.1 Introduction

Numerous synthetic routes towards medium-sized heterocycles have been developed due to their wide natural occurrence and great potential for drug applications. Nevertheless, the preparation of medium-sized rings still represents a synthetic challenge. Cyclization of seven- or eight-membered heterocycles is problematic[5] because of a combination of issues related to enthalpy and entropy. The increase in ring strain and unfavorable interactions are needed to be overcome when the open-chain starting material approaches the ring-shaped transition state. In addition to that, the event of the two chain terminals coming close enough to interact represents the entropy issue. The presence of a carboxylic amide bond in the starting material further complicates cyclization by imposing the restrictions on rotational freedom in non-cyclic precursor and thus preventing the ends of the linear starting material from coming to each other's proximity.

1.2 Nomenclature

The nomenclature of the described heterocyclic compounds is highly inconsistent in literature.

For convinience, the term "oxazepanones" (Figure 1) is used in this work to refer to both substituted 1,4-oxazepan-5-ones and their various unsaturated analogs, usually referred to as oxazepinones. Similarly, term "diazepanones" is used for both 1,4-diazepan-5-ones and their unsaturated counterparts, diazepinones, with different unsaturation degrees.

Likewise, the term "oxazocanones" (Figure 2) is used for both 1,5-oxazocan-4-ones and oxazocinones, whereas the term "diazocanones" refers to substituted 1,5-diazocan-2-one and diazocinones.

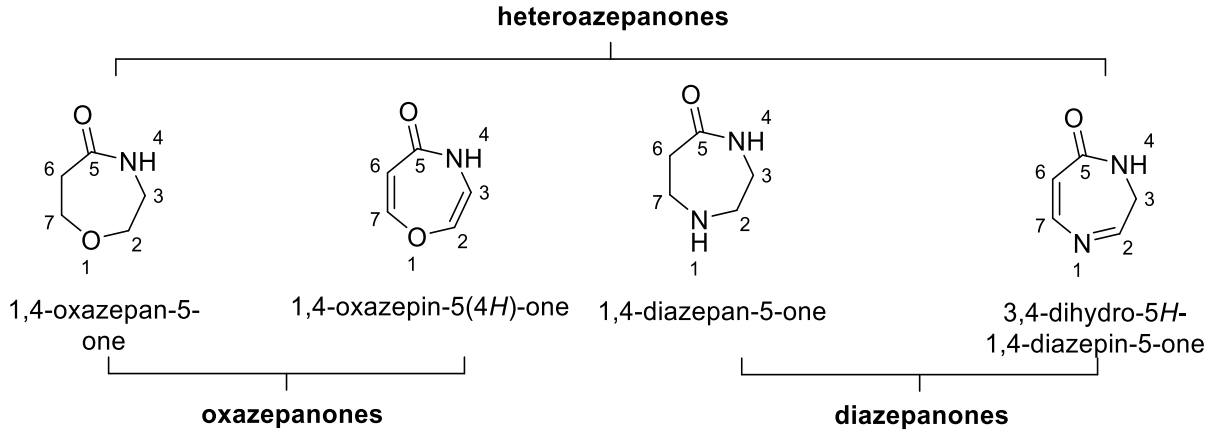


Figure 1. Heteroazepanones

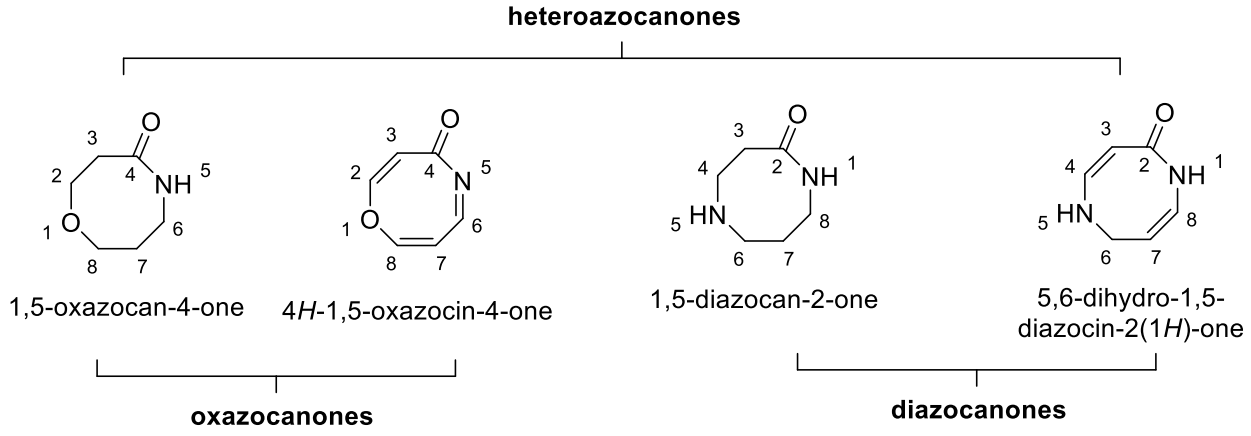


Figure 2. Heteroazocanones

In cases when some statement is applied to both oxazepanones and diazepanones the term "heteroazepanones" is used. Also, the term "heteroazocanones" refers to both oxazocanones and diazocanones.

1.3 Occurrence in Nature and Biological activity

1.3.1 Occurrence in nature

The heteroazepanone moiety is found in a large number of natural products, which possess a broad spectrum of biological activities.[6]

Several natural products have been isolated containing a oxazepanone ring (Figure 3). One example is inducamide C, isolated from a chemically induced mutant strain of *streptomyces sp*. and exhibiting modest cytotoxicity (IC_{50} 10 μM against the NSCLC cell line).[7a] Compound **1**, with a similar lactone core, was isolated from the methanolysis mixture of the marine immunosuppressant lipopeptide microcolin A and shows relatively potent immunosuppressive activity (IC_{50} 8.1 nM of human splenocyte proliferation).[7b] Additionally, a bacterial metabolite was isolated from the Gram-negative bacterium *serratia marcescens* and was identified as serratin, but its biological activities have not been evaluated yet.[8]

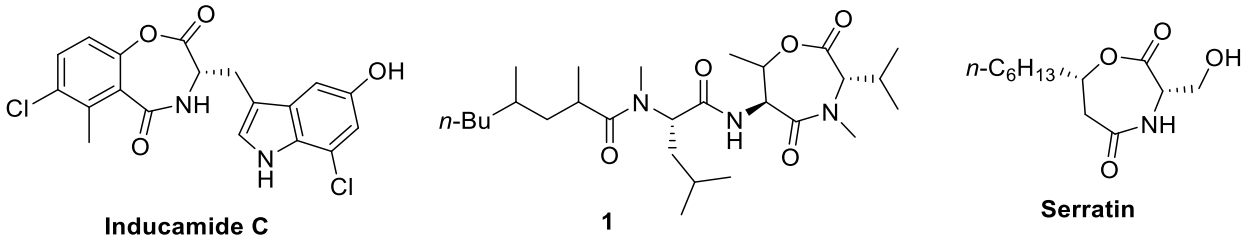


Figure 3. Oxazepanone-containing natural products

The pyrrolo[2,1-*c*][1,4]benzodiazepines (Figure 4) are an established class of heterocyclic antibiotics.[9,10] Since the isolation from cultures of *streptomyces* some members of this class such as tomaymycin (IC_{50} 3 mcg/mL against *escherichia coli* and IC_{50} 0.2 mcg/mL against *bacillus subtilis*), neothramycin A, and anthramycin (MIC of 1.56 μg/ml against *bacillus subtilis* and 0.78

μg/ml against *streptococcus pyogenes*) were shown to be antibiotics with potent antitumor activity. It was shown that neothramycin A also possess capabilities as an antiprotozoal drug, and even possible uses in DNA fluorescence based assays. Sibiromycin[11] is an aminoglycoside antibiotic (MIC of 0.25–2 μg/ml against *staphylococcus aureus*, similar level of activity against *bacillus subtilis* and *escherichia coli*) produced by *streptosporangium sibiricum* that also exhibits antitumour properties.

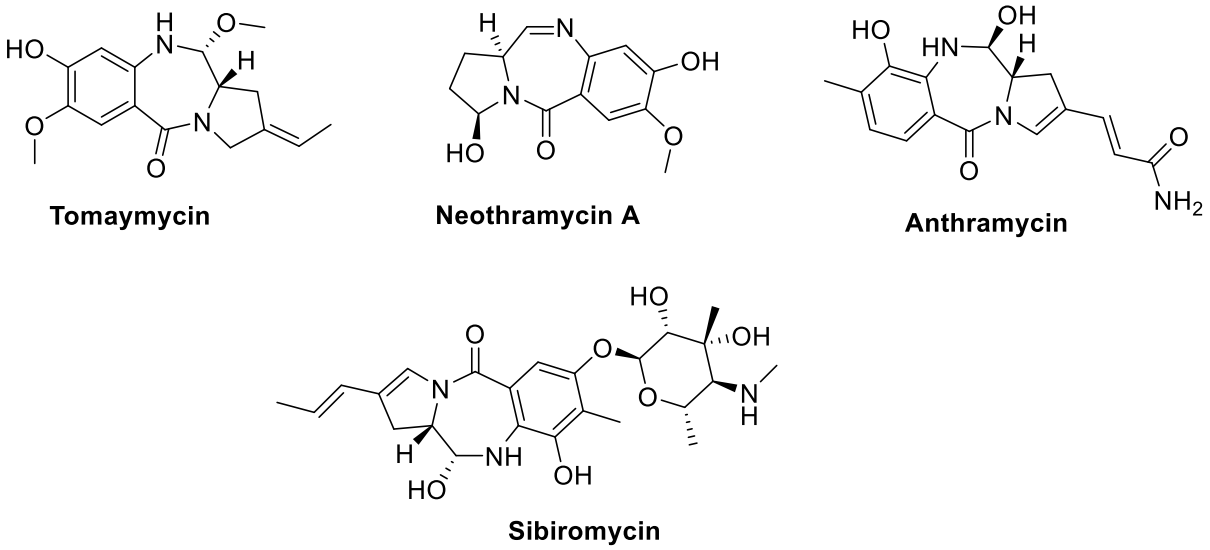


Figure 4. Pyrrolo[2,1-*c*][1,4]benzodiazepines antibiotics

Numerous natural products with the benzodiazepinone core structure (Figure 5) have been isolated and purified. Among them circumdatin alkaloid family isolated from a culture of the fungus *aspergillus ochraceus* displayed a large array of biological activities.[12,13] Moreover, asperlicin is a mycotoxin, derived from the fungus *aspergillus alliaceus*. It acts as a selective antagonist for the cholecystokinin receptor CCKA (ED_{50} of 27.7 μmole/kg in preventing CCK-8 inhibition of charcoal meal gastric emptying in mice), and has been used as a lead compound for the development of a number of novel CCKA antagonists with potential clinical applications.

Additional representatives of this class include benzomalvins A–C (benzomalvins A have shown inhibitory activity against neuropeptide substance P witk *Ki* value at the human neurokinin NK1 receptors) from *penicillium sp,*[14] circumdatins A–G (circumdatins F exhibited an antifouling activity against *bugula neritina* larval settlement with ED_{50} of 8.8 μg/mL) from *aspergillus ochraceus,*[15] and sclerotigenin from *penicillium sclerotigenum*[16] a good number of which are biologically active.

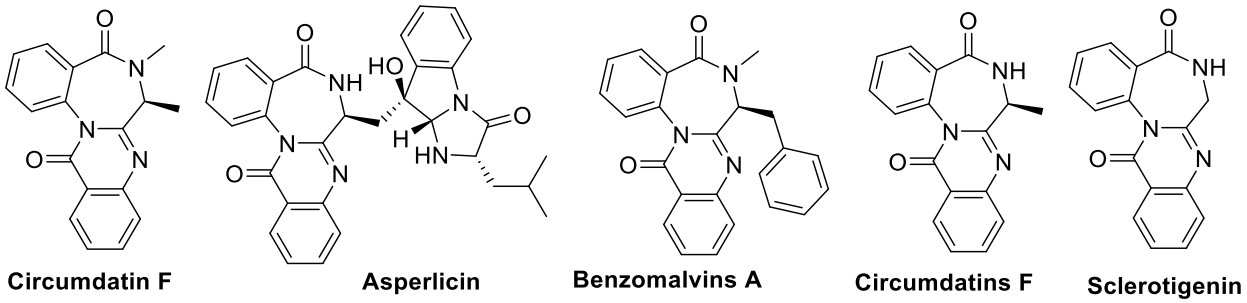


Figure 5. Benzodiazepinone-containing natural products

Examples of naturally-occurring heteroazocanones are scarce. The naturally-occurring homalium alkaloids[17] (Figure 6) were isolated from the *homalium pronyense guillaum* contain diazocanone core are believed to be biogenically-derived from spermine. Even thogh very little is known about the biological role of these unique structures, they have been the targets of many synthetic efforts.

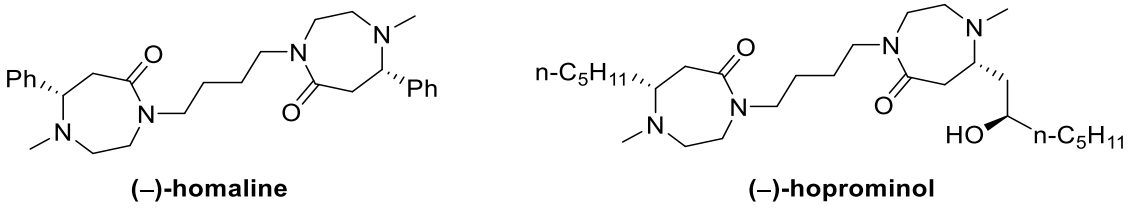


Figure 6. Homalium alkaloids

1.3.2 Medicinal applications and pharmacological activity

Molecules containing heteroazepanone moiety have found both clinical and commercial success. A number of clinically important pharmaceuticals contain seven-membered rings with two heteroatoms. The most common of these compounds incorporate two nitrogen atoms in a 1,4-relationship with an associated aromatic ring.

Pharmacologically active dibenzoheteroazepanes and their structural analogues (Figure 7) containing a heteroaryl-fused heteroazepane ring[6] account for a significant portion of widely prescribed azepine-based drugs. For example, Nitroxazepine (brand name Sintamil) is a tricyclic antidepressant which was reported to be used as an antidepressant agent. It is also indicated for the treatment of nocturnal enuresis. Nevirapine, marketed under the trade name Viramune, is the HIV-1 reverse transcriptase inhibitor used to treat and prevent HIV/AIDS, specifically HIV-1.[18] Pirenzepine (Gastrozepin), an M1 selective antagonist, is used in the treatment of peptic ulcers, as it reduces gastric acid secretion and reduces muscle spasm. Dibenzepin, sold under the brand name Noveril, is a tricyclic antidepressant used for the treatment of depression. Dibenzepin is used mainly in the treatment of major depressive disorder.

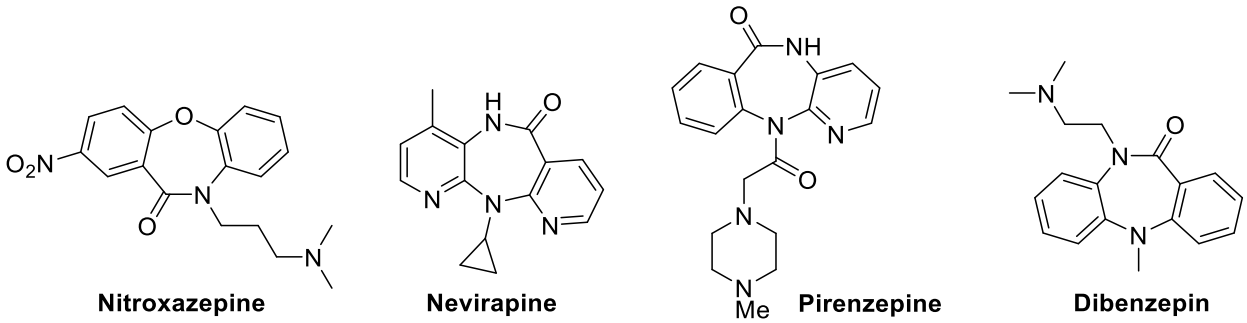


Figure 7. Pharmacologically active dibenzoheteroazepanes and their structural analogues

Other examples of pharmaceutically important benzodiazepanones (Figure 8) include Clobenzepam, an antihistamine and anticholinergic drug, and Diazepinomicin, [19] an antimicrobial alkaloid from a marine *micromonospora sp*., which is a potent inhibitor of the RAS/RAF/MAPK signaling pathway with potential to treat multiple solid tumors.

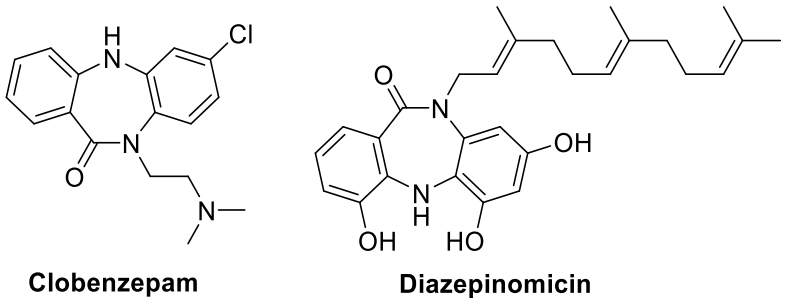


Figure 8. Pharmaceutically important benzodiazepanones

Benzodiazepines (Figure 9) are a class of psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring known to enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor, resulting in sedative, sleep-inducing, anti-anxiety, anticonvulsant, and muscle relaxant properties.[20]

For instance, Bretazenil[21] is an imidazopyrrolobenzodiazepine anxiolytic drug which is derived from the benzodiazepine family. Its high-potency results from high affinity binding to benzodiazepine binding sites where it acts as a partial agonist. Flumazenil[22] sold under the trade name Anexate is a selective $GABA_A$ antagonist. It has antagonistic and antidote properties to therapeutically used benzodiazepines, through competitive inhibition. It is primarily used to treat benzodiazepine overdoses and to help reverse anesthesia. Arfendazam [23] has sedative and anxiolytic effects similar to those produced by other benzodiazepine derivatives, but is a partial agonist at $GABA_A$ receptors, so the sedative effects are relatively mild and it produces muscle

relaxant effects only at very high doses. Lofendazam[23] is an active metabolite of arfendazam which is also used as a human pharmaceutical with sedative and anxiolytic effects. Telenzepine[24] is a thienobenzodiazepane acting as selective M1 antimuscarinic agent. It is used in the treatment of peptic ulcers.

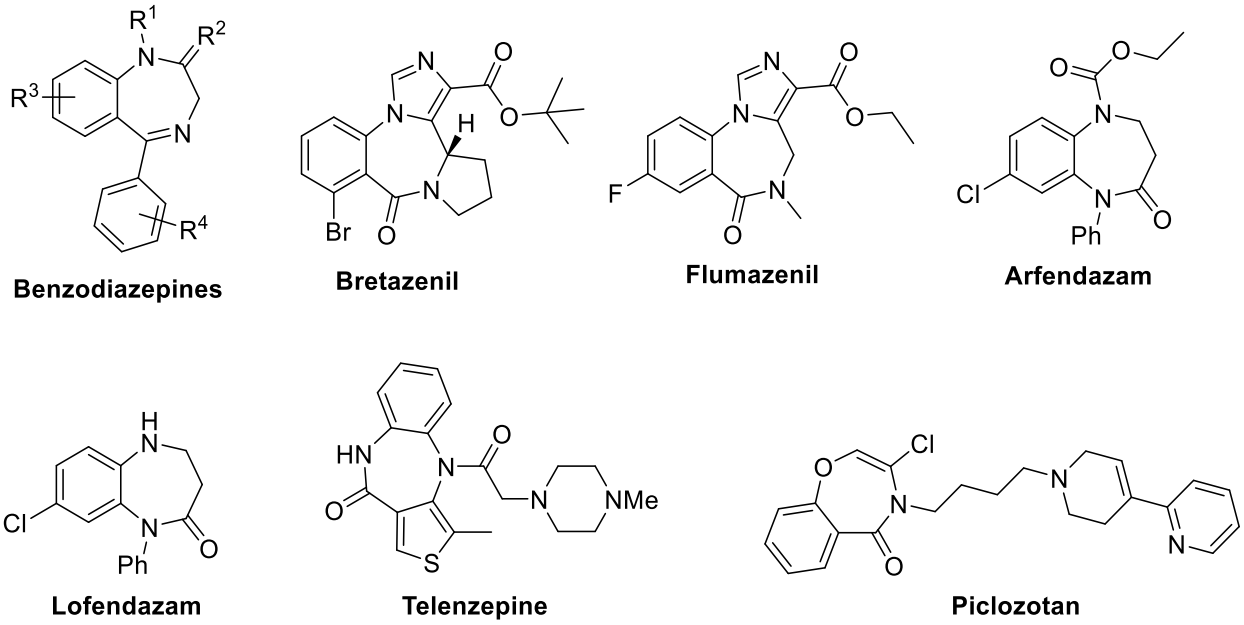


Figure 9. Pharmaceutically important benzoheteroazepanones

Additionally, several benzoxazepanone derivatives[25] (Figure 9) have been found to have highly potent affinity for 5-HT_{1A} serotonin receptor along with good selectivity over dopamine adrenergic receptors. Piclozotan displayed a nanomolar level of activity as a selective 5-HT_{1A} receptor agonist and is currently being developed for treatment of the acute phase of cerebral infarction at phase II in clinical trial.

The unwanted side-effects of the above mentioned naturally occurring antibiotics, pyrrolo[2,1-*c*][1,4]benzodiazepines, led to fruitful research on the synthesis of their analogues (Figure 10). One promising outcome of this research was the work of Wang and co-workers[26] who

designed and synthesized the indole-containing pyrrolobenzodiazepine IN6CPBD and found that this compound exhibited high cytotoxicity against human melanoma and displayed enhanced DNA sequence selectivity. A significant breakthrough was the discovery of pyrrolobenzodiazepine dimers, capable of creating cross-links in the DNA by forming covalent bonds to guanine bases at each end of the molecule, for example SJG-136, which is reported to be in Phase II clinical trials.

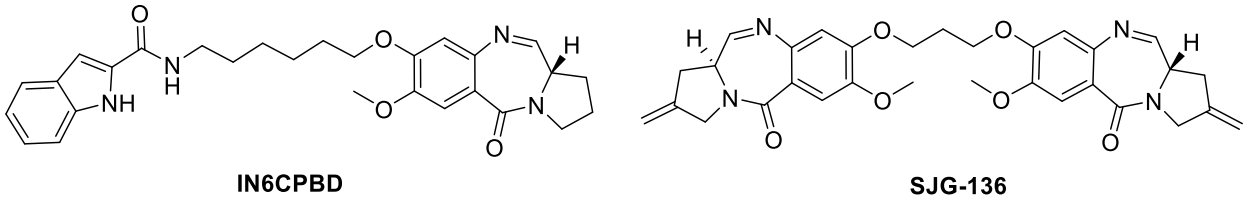


Figure 10. Synthetic pyrrolo[2,1-*c*][1,4]benzodiazepine antibiotics

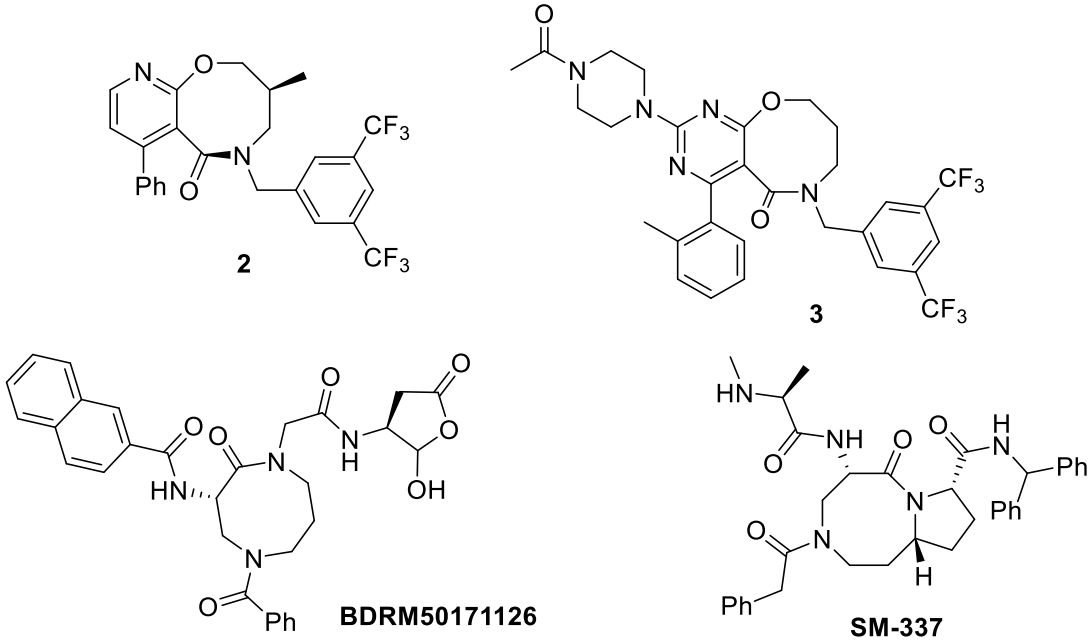


Figure 11. Pharmaceutically significant heteroazocanones

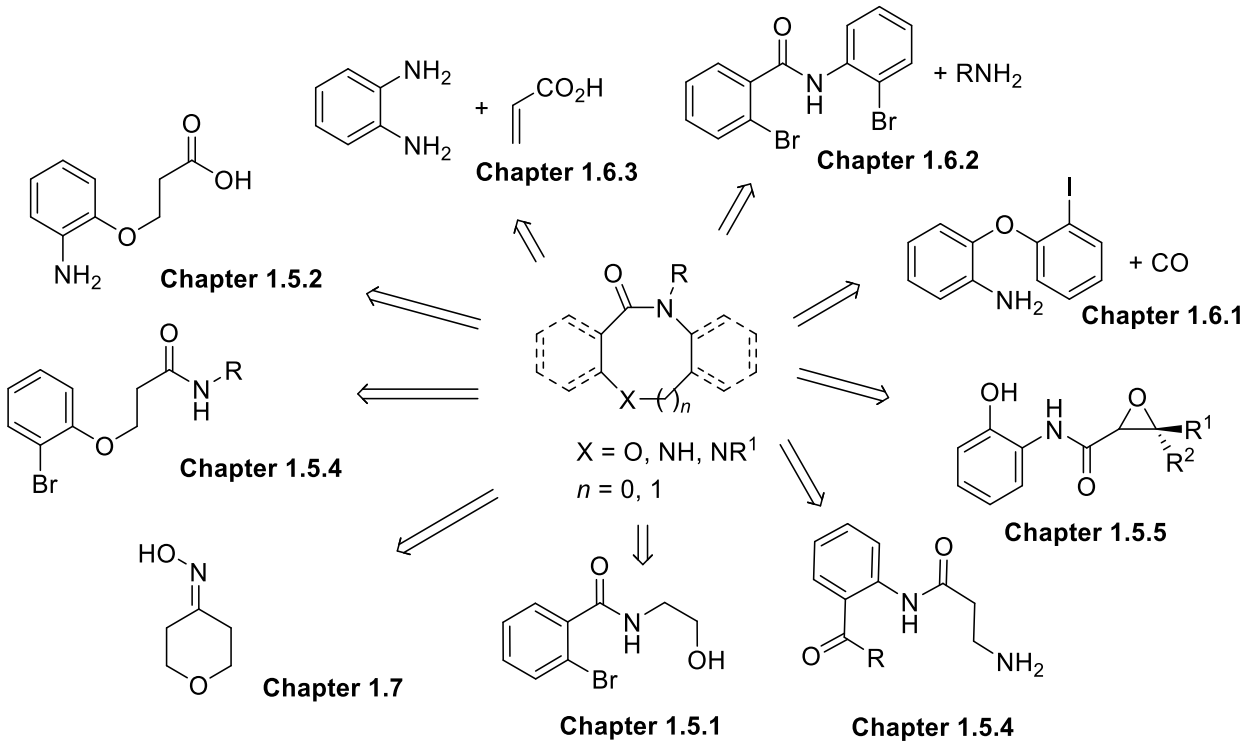
Pharmaceutical applications of heteroazocanones (Figure 11) are more scarce compared to their seven-membered analogs. Nevertheless, some potent Neurokinin receptor NK1 antagonists

possess oxazocanones moiety (**2** and **3**). The eight-membered ring system is known to be an effective core region [27, 28] and it fits well with the NK1 receptor. The diazocanone BDRM50171126 [29] was shown to be active as a selective caspase-1 inhibitor, a class of pharmaceutical agents which have shown promising anti-inflammatory and analgesic activity and are effective in the treatment of rheumatoid arthritis. Another diazocanone-containing drug candidate SM-337 exhibited high potency as a cell growth inhibitor and in induced apoptosis in the MDA-MB-231 cancer cell line.

1.4 Synthetic approaches

Existing routes to heteroazepanones and their analogs containing an eight-membered ring (Scheme 1) largely rely on the preparation of lactams, such as intermolecular acylation of *N*-nucleophiles by carboxylic acid derivatives (Chapter 1.5.2), intermolecular alkylation of primary or secondary amides (Chapter 1.5.4), and ring expansion reactions, including Beckmann and Schmidt rearrangements (Chapter 1.7).

Scheme 1



Another group of methods involves ring closure through the formation of ether or amine moiety by means of nucleophilic substitution (Chapter 1.5.1) or reductive amination reactions (Chapter 1.5.3).

Due to the inherent difficulties of seven- and especially eight-membered ring formation, other more exotic cyclization methods often relying on strain release driven ring opening of small rings were developed (Chapter 1.5.5).

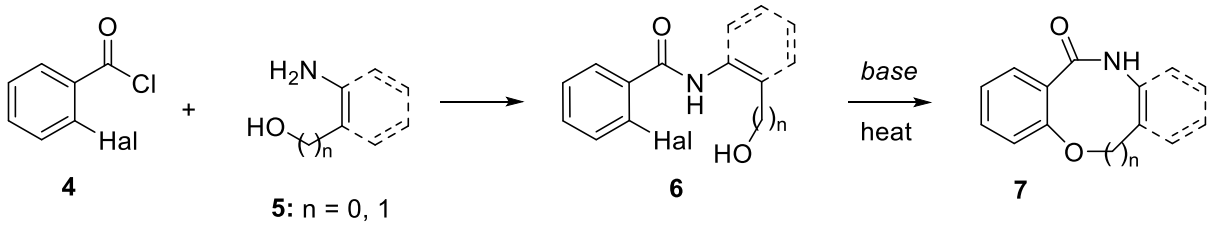
Numerous reported multicomponent methods for assembly of heteroazepanone and heteroazocanone are known. Such methods often utilize carbonylation reactions (Chapter 1.6.1), double aminations (Chapter 1.6.2), or other cyclization methods applied in tandem sequence (Chapter 1.6.3).

1.5 Cyclizations

1.5.1 Intermolecular Nucleophilic Substitution

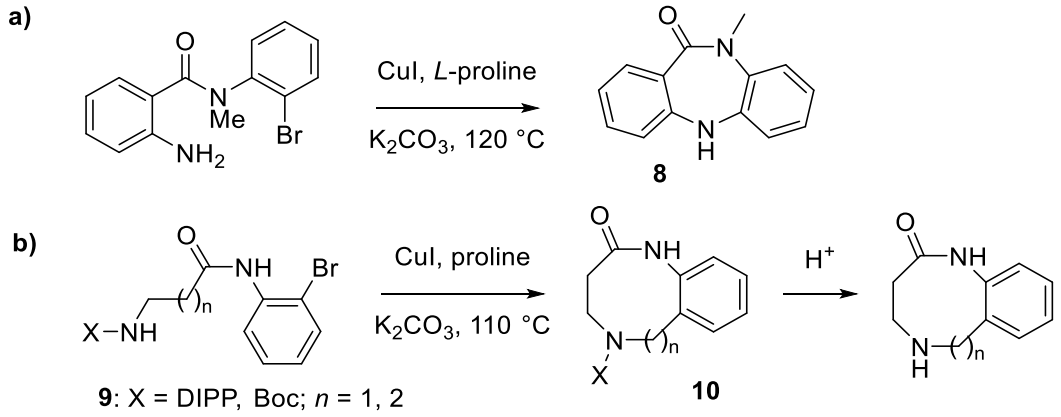
The earliest examples of using intermolecular aromatic substitution (Scheme 2) in the synthesis of benzo- and heteroaryl-fused heteroazepanones and heteroazocanones date to the 1960s. The preparation of oxazepanones[30,31,32] (**7**, n = 0) and oxazocanones[33] (**7**, n = 1) can be achieved through nucleophilic intramolecular cyclization of corresponding aryl halides (**6**) with a base (such as sodium ethoxide or potassium carbonate) in DMF at high temperature (160 – 170 °C). Starting materials (**6**) for such cyclization are commonly prepared by condensation of carboxylic acid derivatives (**4**) and amines (**5**) (See chapter 1.5.2).

Scheme 2



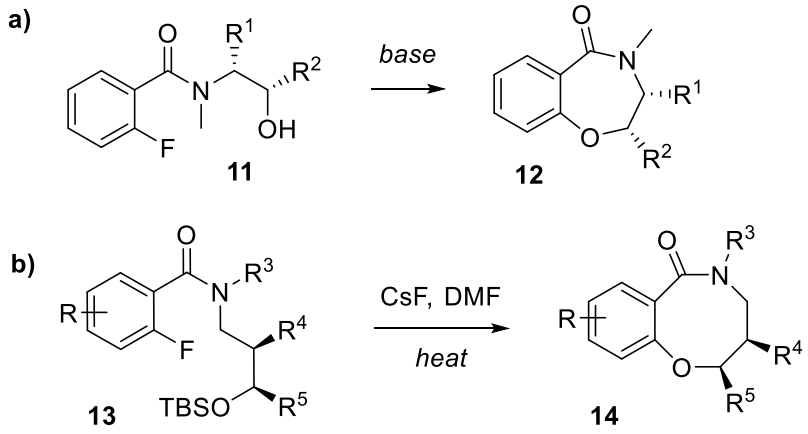
A similar strategy can be employed in the synthesis of diazepanones **8**[34,35] and diazocanones **9** [36] (Scheme 3). For instance, base-mediated CuI/*L*-proline-catalyzed intramolecular aryl amination reaction as the key step was used by Majumdar[35] in the preparation of 1,4-benzodiazepinones **9** (Scheme 3a). Also, Fu[36] has developed an efficient method for the preparation of medium- and large-sized nitrogen heterocycles via copper-catalyzed intramolecular *N*-arylation of phosphoramidates (**9**, X = DIPP) and carbamates (**9**, X = Boc) (Scheme 3b). Introduction of the phosphoryl group or *tert*-butoxycarbonyl at amine nitrogen in **9** was shown to improve intramolecular cyclization under copper catalysis, and this protecting groups can be easily removed under the mild conditions.

Scheme 3



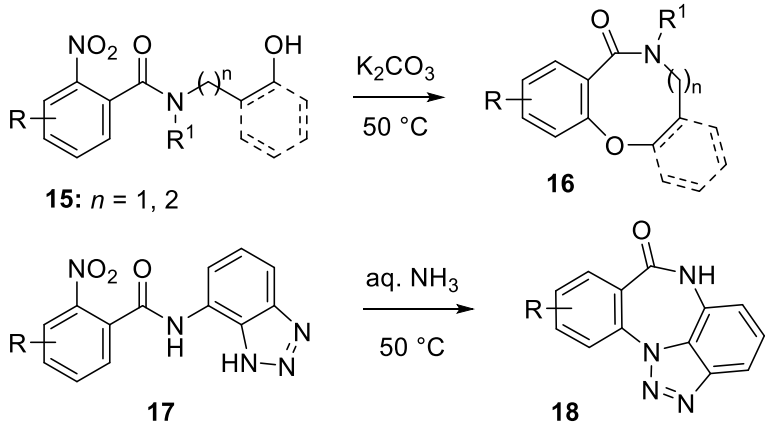
It was further shown that this methodology can be used for preparation of chiral substrates (Scheme 4). [37,38,39,40] For example, Schultz and co-workers[38] have performed intermolecular cyclization of *ortho*-halogen substituted benzamides **11** (derived from chiral 1,2- and 1,3-amino alcohols), by a nucleophilic aromatic substitution process (Scheme 4a).Utilization of tertiary amides resulted in intramolecular cyclization to give benzoxazepanones **12** in good to excellent yields. Similarly, chiral oxazocanones **14** can be prepared via a "one-pot" deprotection/cyclization sequence (Scheme 4b).[39,41] Upon treatment with various sources of basic fluoride (e.g., TBAF, CsF) in DMF at 85 °C, substrates **13** cyclized smoothly to afford the desired eight-membered rings **14** in nearly quantitative yields.

Scheme 4



A common variation of the described protocol utilizes intramolecular nucleophilic displacement of a nitro group in aromatic nitro compounds for preparation of seven- and eight-membered heterocycles (Scheme 5). Samet and co-workers[42] demonstrated that intramolecular nucleophilic displacement of a nitro group in *ortho*-nitrobenzoic acid amides **15** and **17** is a general method of preparing benzannulated seven- and eight-membered heterocycles **16** and **18**.

Scheme 5

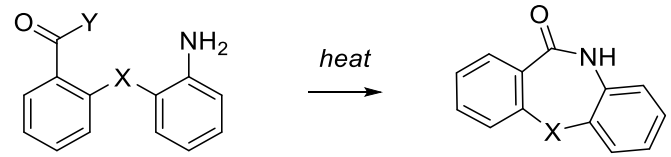


1.5.2 Acylation of Nitrogen Nucleophiles by Carboxylic Acid Derivatives

Historically, methods for synthesis of heteroazepanones and heteroazocanones largely rely on the lactam preparation protocols. Acylation of nitrogen nucleophiles by carboxylic acid derivatives can be considered the most straightforward cyclization method for such heterocycles. The effective synthesis of seven- and in some cases eight-membered rings via direct cyclization has been accomplished. The success of these reactions depends greatly on a ring size mainly due to the unfavorable enthalpic and entropic factors.[43,44]

The earliest examples of employing this methodology for synthesis of diazepanones[45,46] (**20**, X = NH) and oxazepanones[47] (**20**, X = O) date back to the 1960's and 1970's respectively (Scheme 6). It was shown that seven-membered cycles **20** can be produced by direct intermolecular acylation of amino group in **19** with carboxylic acids, esters or acyl chlorides.

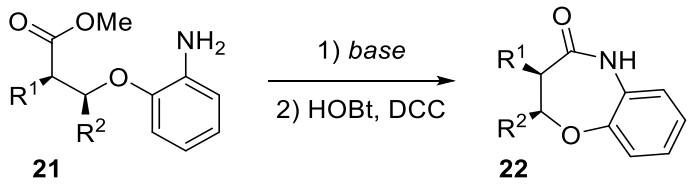
Scheme 6



19: X = OH, NH; Y = OH, OAlk, Hal **20**

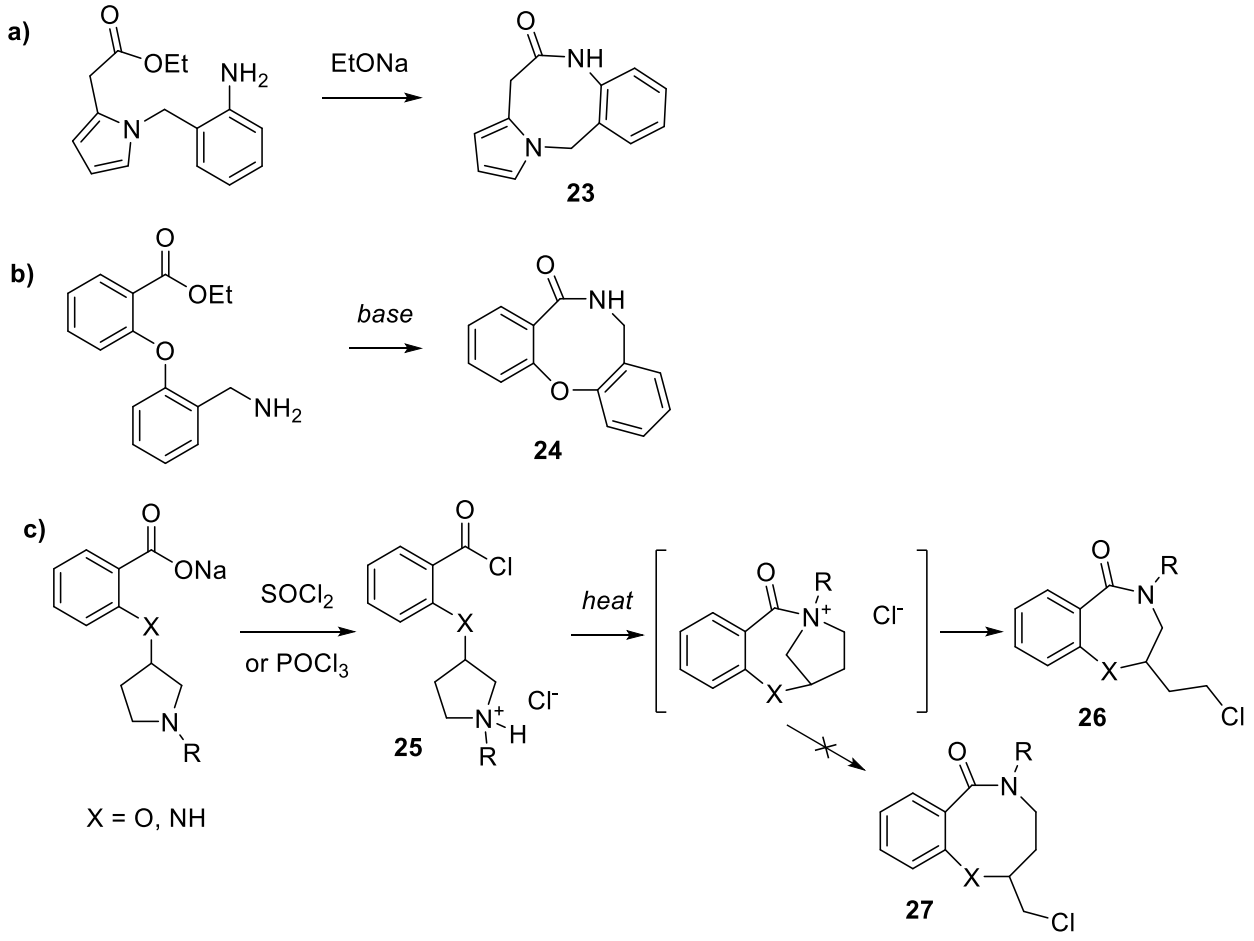
Commonly employed amide coupling reagents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)[48,49] dicyclohexyl carbodiimide (DCC),[50] and 1-hydroxybenzotriazole (HOBt)[51] can be used to facilitate the desired cyclization under mild conditions thus broadening the substrate scope of the reaction. For instance, optically active benzoxazepanes **22** can be prepared from chiral aminocarboxylic acid derivatives **21** by cyclization using DCC and HOBt (Scheme 7).[52,53]

Scheme 7



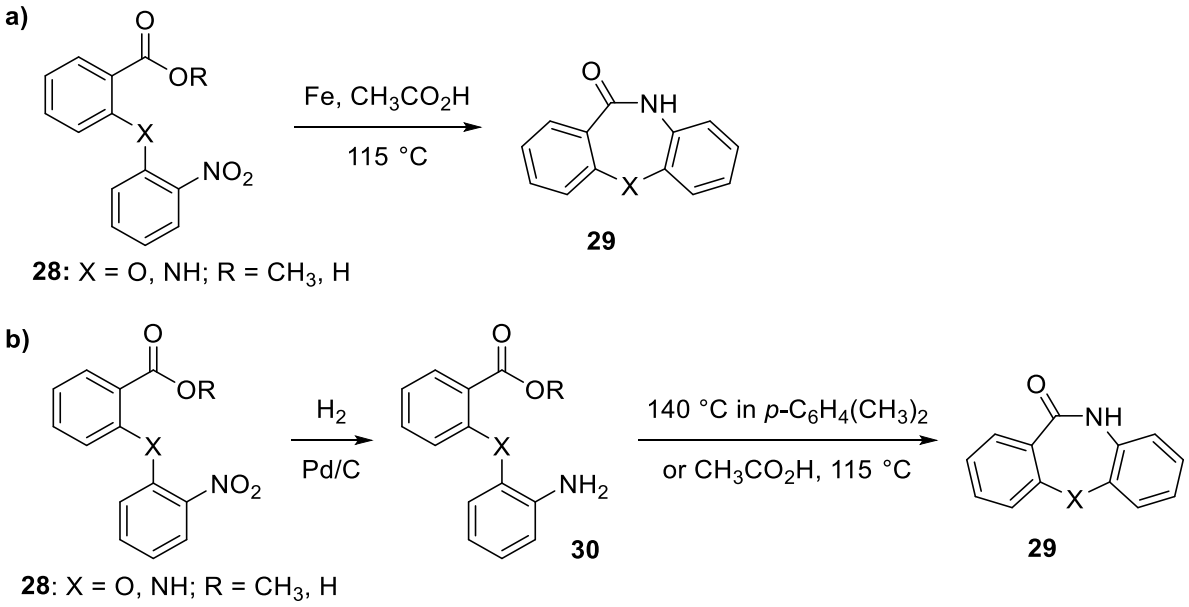
Application of intramolecular amide coupling in synthesis of heteroazocanones (Scheme 8) is more scarce due to the unfavorable entropic factors of eight-membered ring closure[5]. Examples of this approach can be can be seen in the work by Korakas and Varvounis[54] on synthesis of pyrrolobenzodiazepanes **23** (Scheme 8a) or in the report by Liebigs and co-workers[55] showing preparation of dibenzoazocanes **24** (Scheme 8b). Preferential formation of seven-membered rings over eight-membered rings can also be shown using the example of work by Cale et al. (Scheme 8c).[56] Intermolecular acylation of tertiary amides **25** was followed by rearrangement yielding seven-membered lactams **26** exclusively, whereas eight-membered lactams **27** were not observed.

Scheme 8



Bunce and Schammerhorn[57] have developed a common variation of such acylative cyclization protocol (Scheme 9a). Various dibenzo-fused oxazepanones (**29**, X = O) and diazepanones (**29**, X = NH) were successfully obtained via a tandem reduction–lactamization reaction under dissolving metal conditions using iron and acetic acid. Tandem reactions involving reduction of an aromatic nitro group of **28** and trapping the aniline nitrogen with a suitably positioned carbonyl-containing functionality using iron powder in acetic acid at 115 °C affords the target heterocycles in >90% yield. It was also demonstrated that catalytic hydrogenation would not furnish the desired lactam (**29**) formation from these substrates (**28**) (Scheme 9b). Isolated products of simple reduction of the nitro group (amino compounds **30**) can be heated in xylene at 140 °C to effect lactam formation.

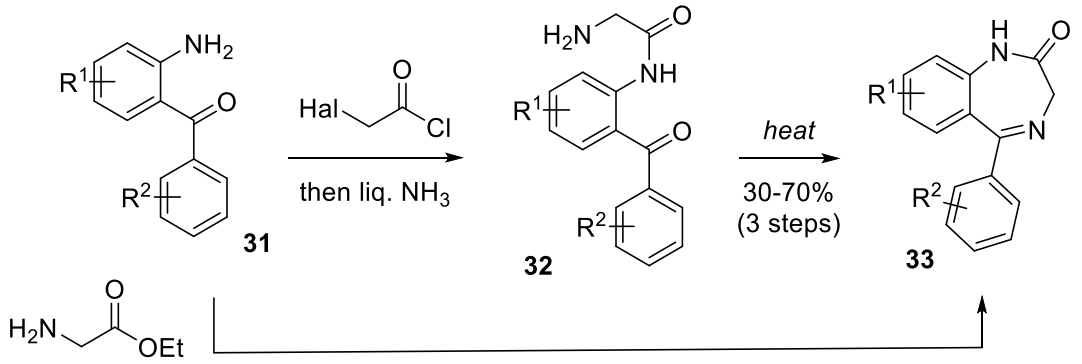
Scheme 9



1.5.3 Schiff base condensation

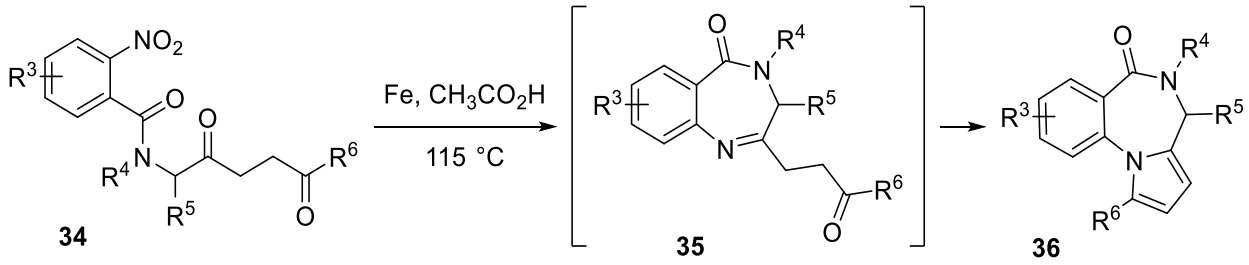
A widely applicable method for the synthesis of diazepanones and diazocanones by intermolecular reaction between amines and carbonyl compounds is shown in Scheme 10. A three-step procedure has been employed by Kassiou[58] starting from the *ortho*-aminobenzophenone **31** with the aniline nitrogen first acylated with a haloacetyl halide to give corresponding amides and subsequent aminolysis affording α-aminoamides **32**. Following intramolecular Schiff base condensation afforded the benzazepanes **33** in 30–70% yields over three steps. It was further demonstrated that a single-step method can be employed using the same *o*-aminobenzophenones **31** with a glycine ester hydrochloride to afford the target benzodiazepinone-type structures **33** in similar yields.

Scheme 10



A similar strategy was employed by Butin et al. for making pyrrolobenzodiazepanes **36** (Scheme 11).[59] Their method is based on a one pot reduction of the nitro group in **34** to amino group and subsequent cyclization with concomitant formation of the diazepine and pyrrole rings. Reduction of corresponding *ortho*-nitrobenzamides **34** in glacial acetic acid with iron powder produced non-isolable amines that cyclized spontaneously to afford intermediate benzodiazepines **35** which underwent another cyclocondensation to afford target pyrrolobenzodiazepanes **36**.

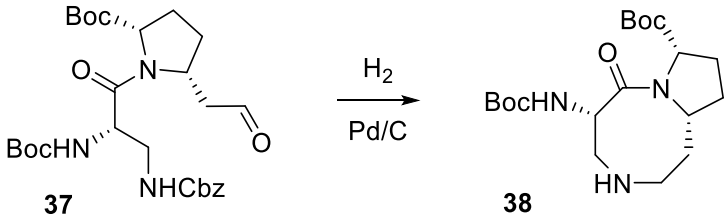
Scheme 11



It was also demonstrated that Schiff base condensation methodology can be applied to form the eight-membered ring of diazocanones (Scheme 12). For instance, Wang et al.[60] performed a tandem palladium-catalyzed hydrogenative conditions sequence that included reductive Cbz-deprotection of **37** followed by condensation of the exposed amino group with the nearby aldehyde

group. The corresponding imine was readily reduced under reaction conditions to provide the desired product **38**.

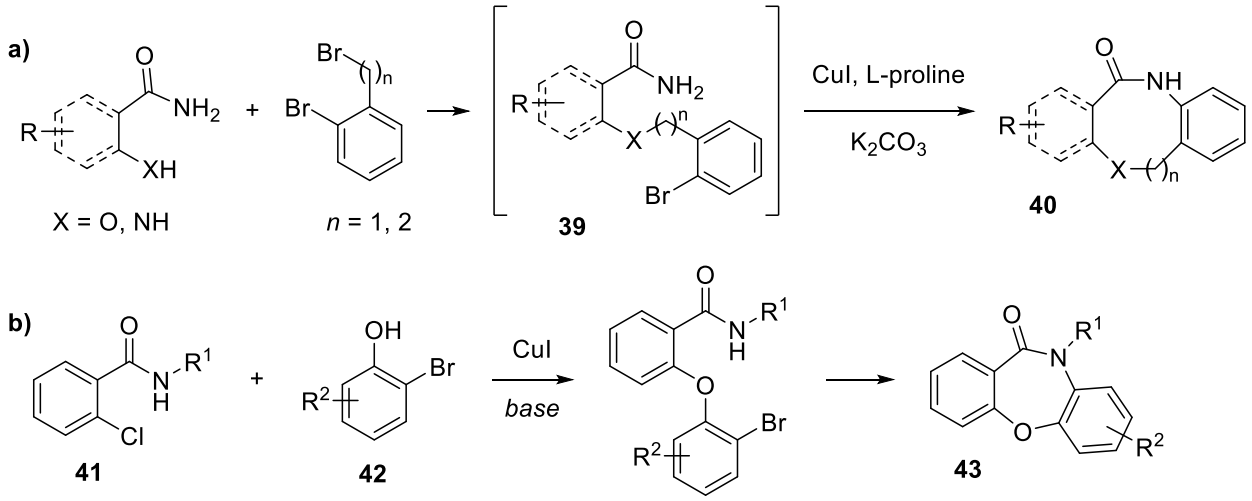
Scheme 12



1.5.4 Amide alkylation

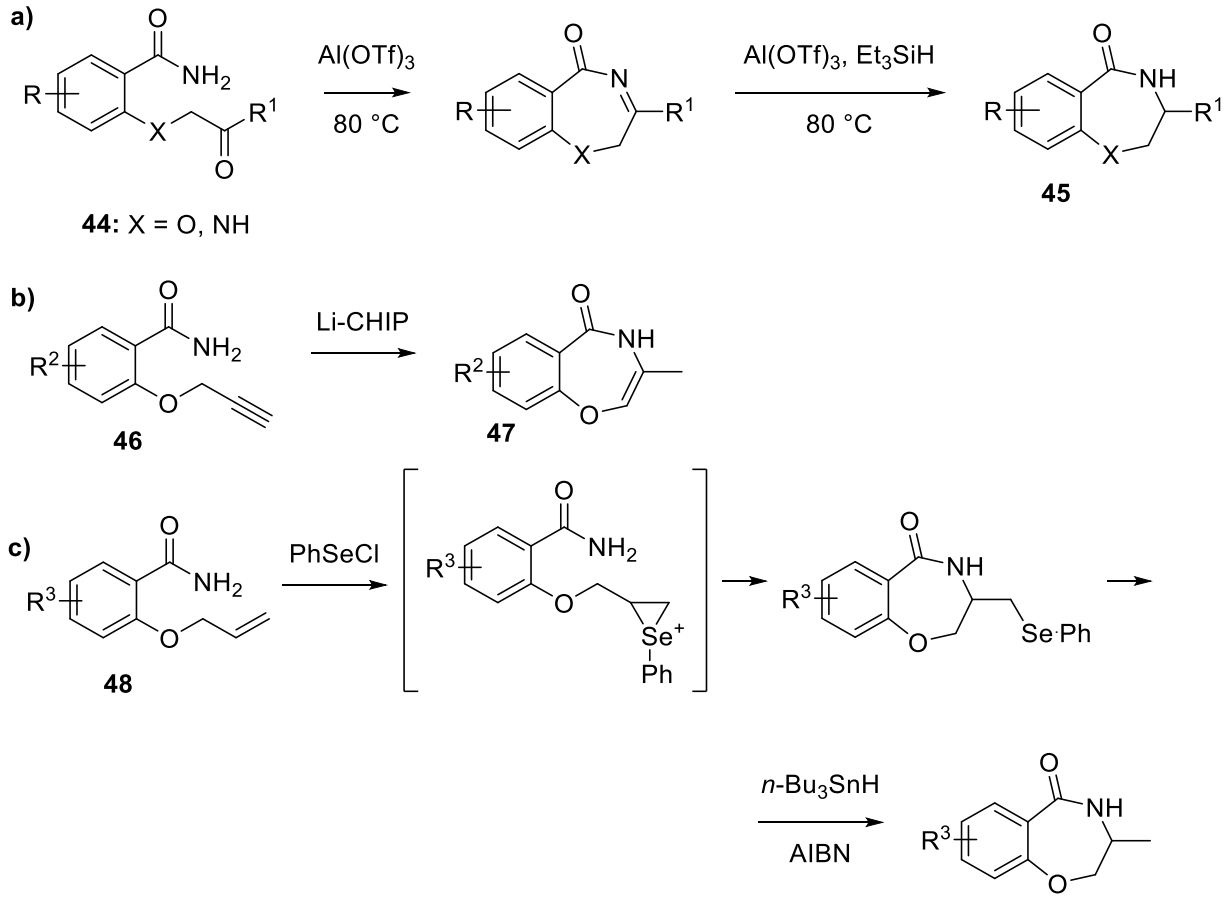
Ring closure through intermolecular alkylation of primary and secondary amides can be viewed as one of the alternative methods of heteroazepanone and heteroazocanone synthesis. An example of a strategically straightforward way of using this method was realized by Al-Tel et al. (Scheme 13a).[61] Modular CuI-*L*-proline catalyzed strategy for the synthesis of starting materials for eight- and nine-membered heteroatom ring systems (**39**) followed by base-mediated ring closure furnished various oxazocanones (**40**, X = O) and diazocanones(**40**, X = NH). Similarly, oxazepanones **43** can be made from *N*-substituted-*o*-chlorobenzamides **41** and *o*-halogenated phenols **42** (Scheme 13b).[62]

Scheme 13



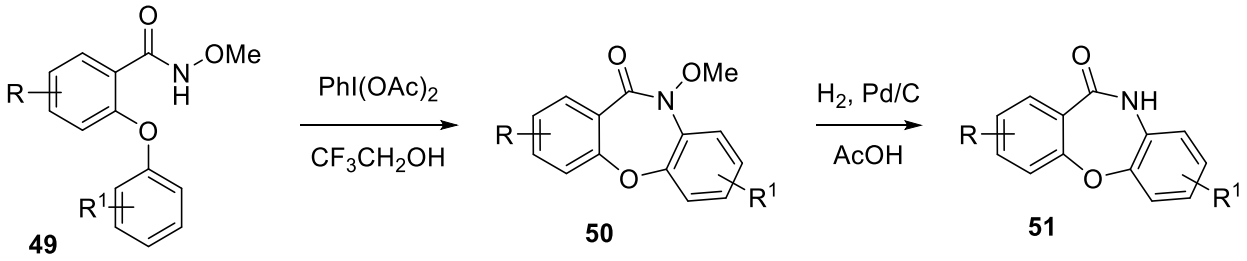
Some alternative methods of amide alkylation include using tethered ketones, double or triple bonds (Scheme 14). A facile and versatile synthesis of oxazepanones (**45**, X = O) and diazepanones (**45**, X = NH) from ketoamides **44** via $Al(OTf)_3$-mediated cascade cyclization and ionic hydrogenation using the Et_3SiH has been developed by Yin (Scheme 14a).[63] In the work by Schmid and co-workers[64] *ortho*-(2-propynyl)oxybenzamides **46** were cyclized under base catalysis to furnish seven-membered rings **47** (Scheme 14b) and lithium cyclohexylisopropylamide (Li-CHIP) in *N*-methylpyrrolidone was shown to be most efficient. It was also demonstrated by Ueda that appropriate *ortho*-allylaminobenzamide derivatives **48** can be used in an intermolecular cyclization using benzeneselenenyl chloride (Scheme 14c).

Scheme 14



An interesting method for construction of the dibenzoxazepanone skeleton from the readily available substituted *ortho*-(aryloxy)benzamides **49** through an intramolecular cyclization involving a direct oxidative C–N bond formation in the final step was shown by Du.[65] As illustrated in Scheme 15, the *N*-methoxy oxazepanones **50** could be readily converted to *N*-unsubstituted oxazepanone **51**, through a palladium catalyzed hydrogenation reaction, which allows for the further derivatization of the free NH moiety.

Scheme 15

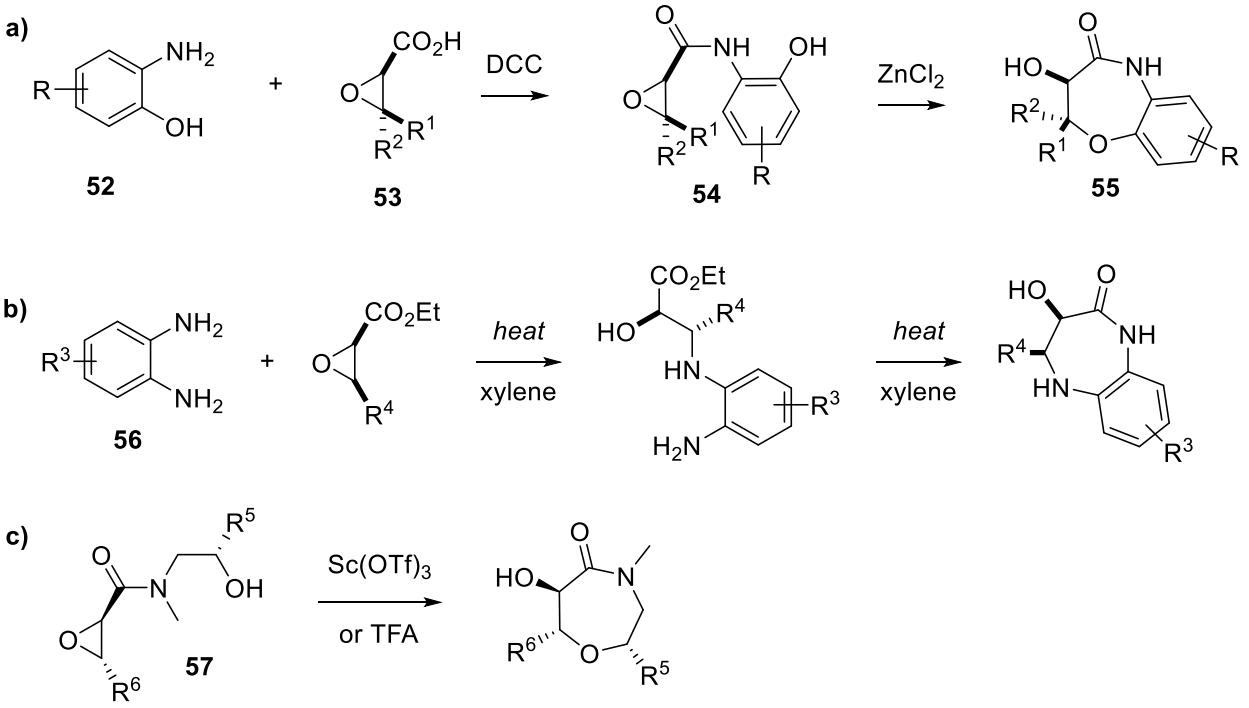


1.5.5 Other ring closure methods

Due to the unfavorable enthalpic and entropic factors[43,44] the effective synthesis of seven- and especially eight-membered rings often rely on more exotic cyclization methods. Among them using strain release energy of small rings is one of the most dominant. Cyclizations described in Chapters 4 and 5 naturally fall into this category.

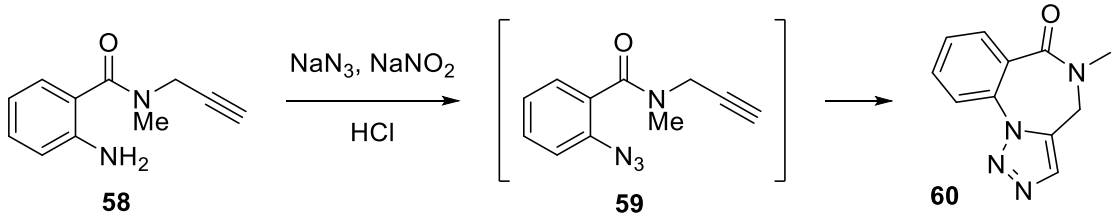
An efficient two-step preparation of chiral oxazepanones **55** and oxazocanones starting from aminoalcoholes **52** and oxiranecarboxylic acid derivatives **53** (Scheme 16a) was initially discovered by Liebscher[66] and further developed by Ohnmach and co-workers.[67] Cyclization of substituted oxiranecarboxamides **54** in the presence of $ZnCl_2$ furnished the desired seven-membered cycles **55** in excellent yields. In all cases these cyclizations occurred with inversion of configuration. The effect of $ZnCl_2$, in the product formation is believed to be the coordination of the zinc ion at NH and the oxirane oxygen atom activating the oxirane ring and directing the attack of the phenolic OH to the ß-position. It was further demonstrated that the same methodology can be applied to the broad range of chiral ethanolamines **57**[67] (Scheme 16c) and *ortho*-phenylenediamines **56**[68] (Scheme 16b). The most efficient catalyst identified for the ring closure of the intermediate epoxyamides was found to be the $Sc(OTf)_3$.

Scheme 16



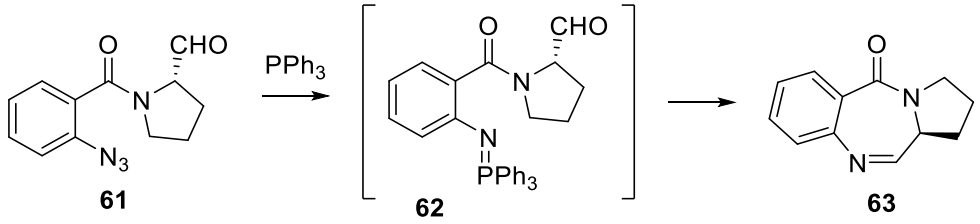
As demonstrated by Broggini,[69a] *ortho*-aminobenzamides **58** containing propynyl substituent on the amide nitrogen can serve as readily accessible precursors for the oxazocanone core (Scheme 17). For example, diazotization of aniline nitrogen of **58** and in situ azide (**59**) formation by addition of sodium azide, followed by heating the resulting mixture under reflux in toluene, afforded the tricyclic product **60** in moderate yield. Thomas[69b] has shown that same sequence involving diazotization, azide addition followed by 1,3-dipolar cycloaddition reaction can be performed using polymer supported carbodiimide.

Scheme 17



An intramolecular aza-Wittig reaction of the appropriately substituted phosphanimine **61** was utilized by Molina[70] as a key step in synthesis of a pyrrolobenzodiazepane ring system (Scheme 18). This approach allows cyclization of the diazepane ring (**63**) to occur under neutral and extremely mild reaction conditions and involves a simple work-up procedure. Staudinger reaction of azides **61** with tertiary phosphines directly led to the pyrrolo[2,1-*c*][1,4]benzodiazepanes **63** in yields of 90% and above at 0 °C and the conversion was completed in 1 hour. Moreover, when the highly reactive tributylphosphine was used as a cyclization agent, formation of intermediate **62** was performed at lower temperature (–10 °C) and completion of the cyclization reaction required a shorter period of time (30 minutes).

Scheme 18



1.6 Multicomponent and tandem methods

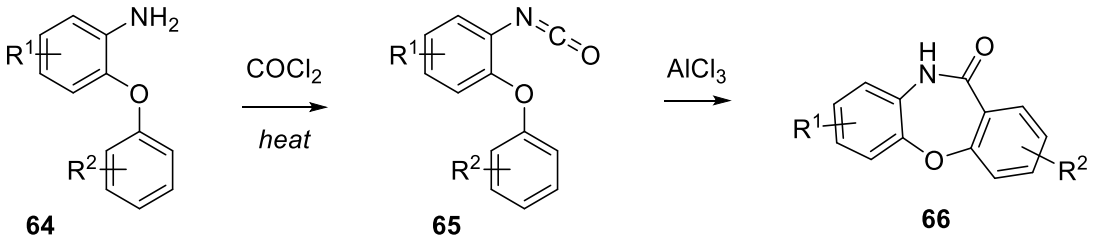
1.6.1 Carbonylation reaction

Several strategies of constructing medium ring heterocycles involving carbonylation reaction with phosgene or transition metal-catalyzed transformations with different CO sources are described in literature.

In 1982, Nagai[71] reported an intermolecular acylation of *ortho*-isocyanatophenoxybenzenes **65**, affording dibenzoxazepanones **66** in good yield (Scheme 19). Treatment of substituted *ortho*-

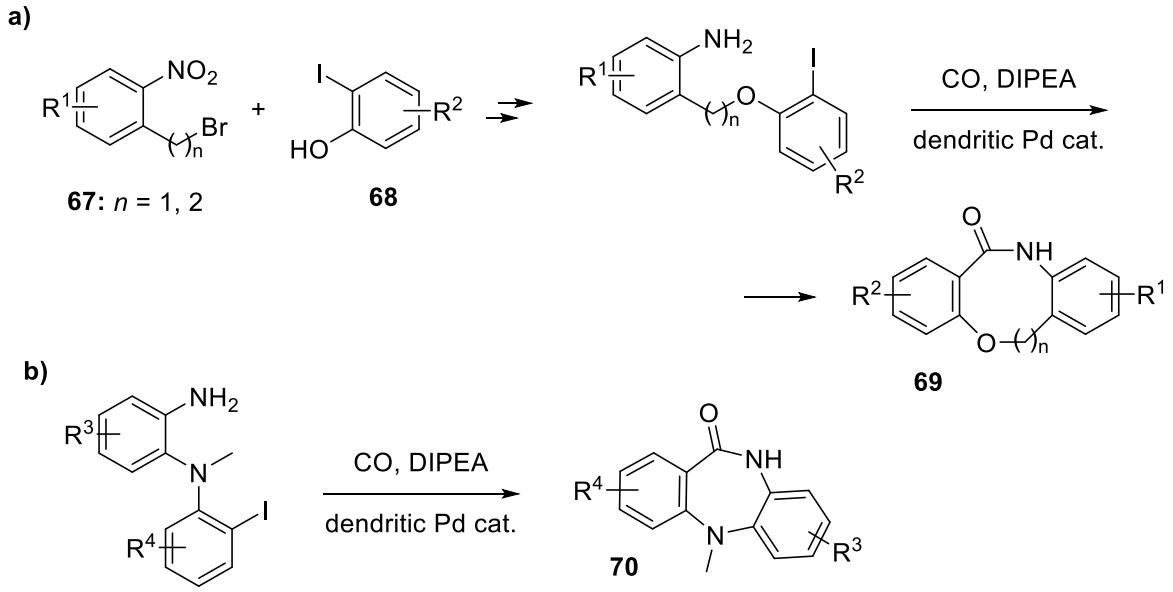
aminophenoxybenzene starting materials **64** with phosgene, followed by cyclization with aluminum trichloride, afforded the desired oxazepanones **66**. Likewise, both stages of this sequence can be performed in one pot if *o*-dichlorobenzene is used as a solvent, as demonstrated by Wagh.[72]

Scheme 19



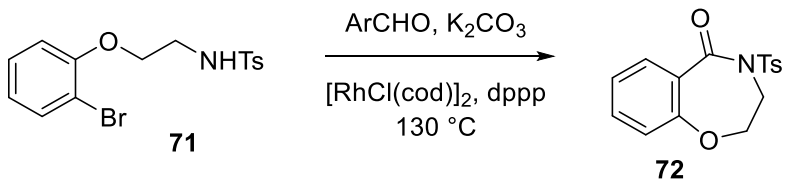
An intramolecular carbonylation reaction has been performed by Lu and Alper[6c], using appropriately substituted *ortho*-iodophenols **68** and nitrobenzenes **67** as starting materials and palladium-complexed dendrimers supported on silica (Scheme 20). The results showed that dendritic catalysts display high activity, affording oxygen (Scheme 20a) or nitrogen-containing (Scheme 20b) seven- or eight-membered ring fused heterocycles **69** an **70** in excellent yields. The transition-metal-catalyzed carbonylation reaction is a powerful tool in organic chemistry, however the difficulties associated with the separation of products from the reaction mixture and the recovery of the expensive, and sometimes toxic, catalysts are major drawbacks in these transformations. However, it was demonstrated that proposed silica-supported catalysts can be easily recovered by simple filtration in air and reused for up to eight cycles with only a slight loss of activity. The wide functional group compatibility of this carbonylation method was further demonstrated: reaction was shown to tolerate fluoro, chloro, methoxy, acetyl, and methoxycarbonyl groups.

Scheme 20



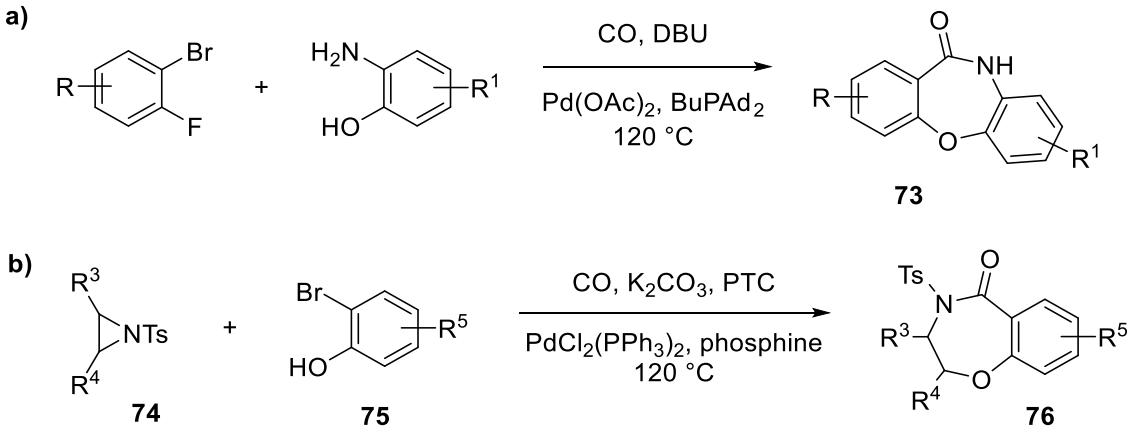
Morimoto and co-workers [73] designed conceptually similar CO gas-free carbonylative cyclization of organic halides **71**, with tethered nucleophiles using aldehydes as a substitute for carbon monoxide (Scheme 21). It was shown that described rhodium-catalyzed transformation can be used to access substituted oxazepanones **72**. Elimination of the need for the direct use of carbon monoxide, achieved by utilizing various organic and inorganic carbonyls as a substitute for carbon monoxide makes carbonylation more experimentally simple and easy to use.

Scheme 21



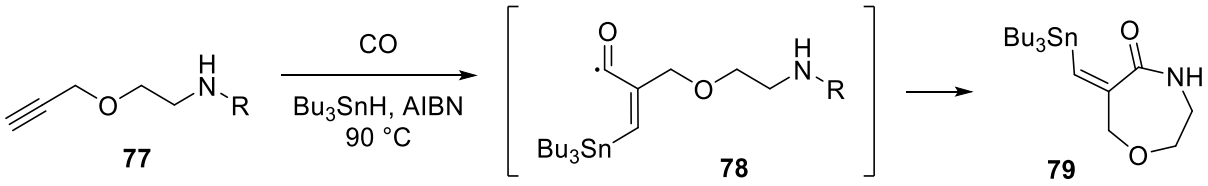
A base-mediated one-pot protocol for the modular synthesis of diversely-substituted benzoxazepanones **73** has been developed by Shen and Wu (Scheme 22a).[74] The desired transformation is achieved through an aromatic nucleophilic substitution (S_NAr, *O*-arylation) followed by aminocarbonylation and spontaneous cyclization. Another one-pot synthesis of a broad range of oxazepanone substrates that relies on transition metal-catalyzed carbonylation was described by Chouhan and Alper (Scheme 22b).[75] This domino process includes ring-opening/carboxamidation reactions of various *N*-tosylaziridines **74** with a range of *ortho*-halophenols **75** under phase-transfer catalysis. The method was shown to be compatible with a range of cyclic or acyclic *N*-tosylaziridines **74** and *ortho*-halophenols or pyridinols **75** providing facile access to a variety of benzo- and pyrido-oxazepanones **76**.

Scheme 22



In the work by Ryu and co-workers[76] oxazepanone ring (**79**) formation is achieved through a new carbonylative annulation method for five- to seven-membered ring lactam synthesis (Scheme 23). Intermolecular substitution at nitrogen by α,β-unsaturated acyl radicals **78** (generated in situ from a variety of substituted *N*-phenethylalkynylamines **77**) took place accompanied by elimination of an phenethyl radical.

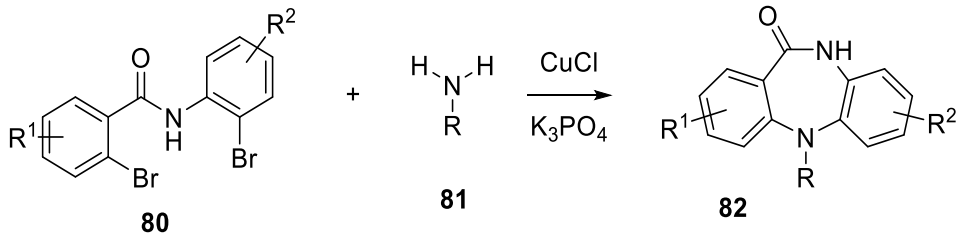
Scheme 23



1.6.2 Double amination

Intermolecular copper-catalyzed double amination of aryl bromides **80** can proceed to afford substituted diazepanones **82** as demonstrated by Ma et al. (Scheme 24).[77] *N*-Aryl aminocarbonyl groups was shown to greatly promote the copper-catalyzed coupling of aryl halides with amines. Therefore, double coupling reactions of dibromides with primary amines **81** offers an alternative direct pathway for preparing medium-sized rings under mild conditions.

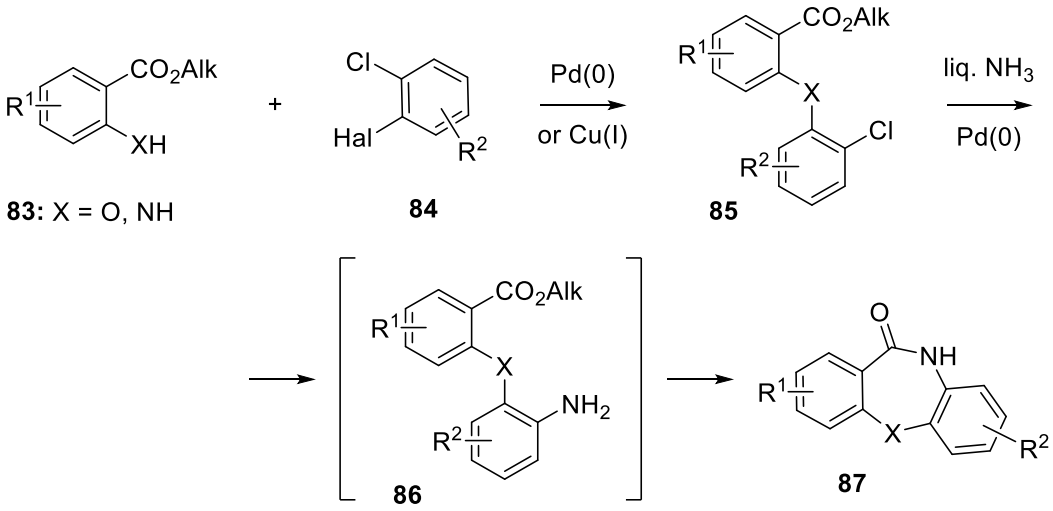
Scheme 24



A general and highly efficient protocol for the synthesis of dibenzo-fused oxazepanones, diazepanones, and their structural analogues was reported by Tsvelikhovsky and Buchwald (Scheme 25).[78] In the presence of catalytic quantities of palladium, readily accessible anilines (**83**, X = NH) or phenols (**83**, X = O) containing ester functionality in *ortho* position and 1,2-dihaloarenes **84** were cross-coupled in the presence of ammonia to provide intermediate **86** and then spontaneous intramolecular condensation occurred to furnish the corresponding seven-

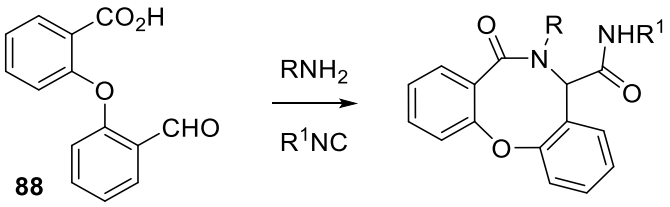
membered ring of **87** in one step. This synthetic strategy is based on the assumption that at the reaction condition, initially formed precursor **85** would generate intermediate **86** via cross-coupling with ammonia and then further spontaneously undergo an intramolecular condensation to form the corresponding dibenzodiazepanones (**87**, X = NH) and dibenzoxazepanones (X = O).

Scheme 25



A conceptually similar approach can be realized using primary amine substrates. For example, a large diversity can be quickly achieved in the three-component synthesis based on the Ugi reaction using bifunctional starting materials **88** containing aldehyde and carboxylic acid as reported by Zhang (Scheme 26).[79]

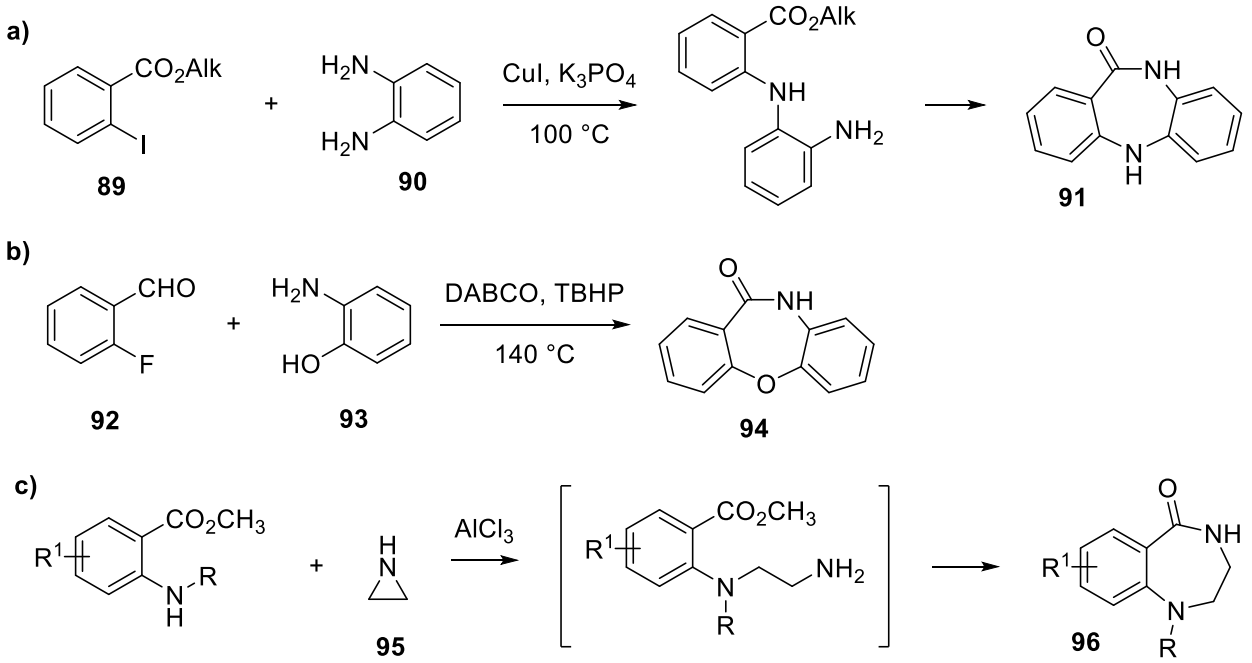
Scheme 26



1.6.3 Other multicomponent methods

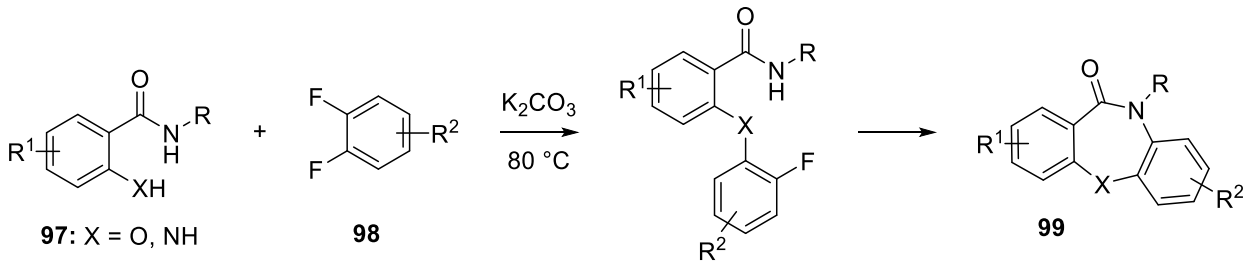
Numerous reported multicomponent methods of heteroazepanone and heteroazocanone synthesis rely on utilizing cyclization methods previously described in Chapter 1.5 in tandem sequence. For instance, dibenzodiazepinones **91** can be prepared in one pot from ethyl *ortho*-iodobenzoates **89** and *ortho*-phenylenediamines **90** (Scheme 27a). Initial nucleophilic substitution and subsequent intramolecular acylation can be achieved using combination of CuI and K_3PO_4.[80] It was also demonstrated by Wu[81] that *ortho*-halogenated benzaldehydes **92** can be used as reaction partners for *ortho*-aminophenoles **93** under oxidative conditions to allow the formation of dibenzo-fused oxazepanones **94** (Scheme 27b). In a conceptually similar transformation reported by Vega[82] a nucleophilic attack on aziridine **95** followed by an intermolecular acylation provides expedited access to diazepanones **96** (Scheme 27c).

Scheme 27



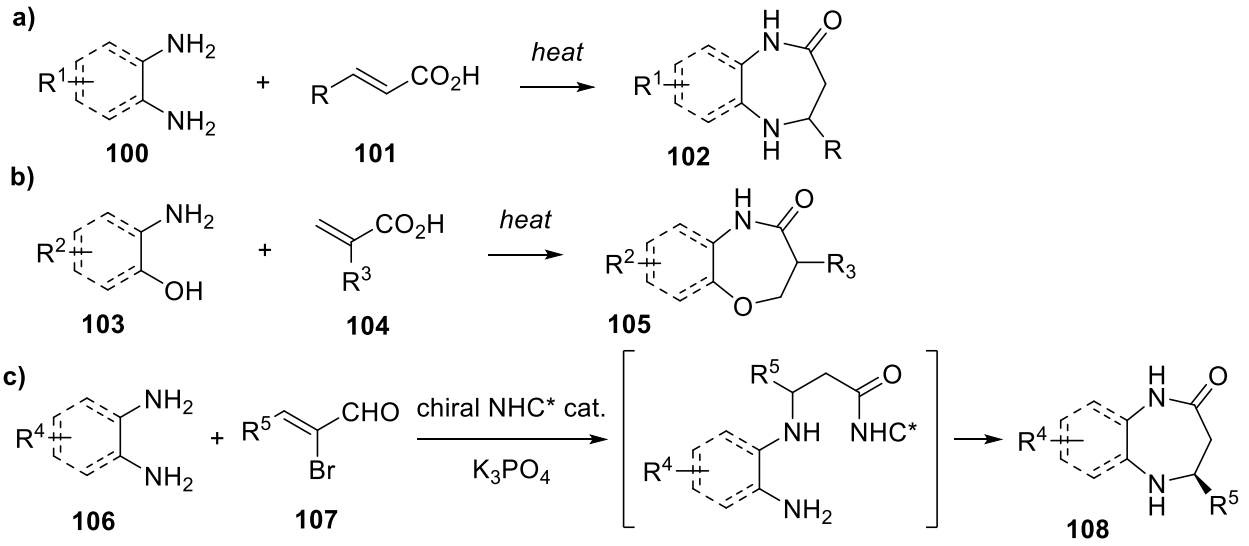
Another group of bicomponent methods also relying on nucleophilic substitution as a first step, uses amide alkylation in order to cyclize initially formed intermediates. For example, Ma[83] reported an effective regioselective synthesis of fused oxazepanone skeleton (**99**, X = O) from commercially available *N*-substituted salicylamides (**97**, X = O) and 1,2-difluorobenzenes **98** (Scheme 28). It was further shown[84] that the same method is similarly efficient for the synthesis of benzodiazepines (**99**, X = NH) from *ortho*-aminobenzamides (**97**, X = NH).

Scheme 28

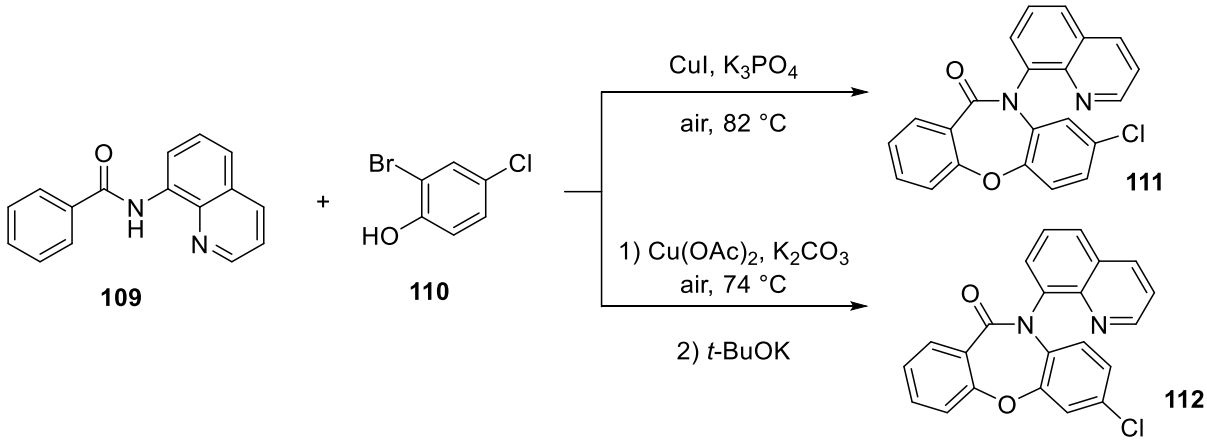


An inherently elegant reaction between acrylic acid derivatives (**101**, **104**) and aminoalcohols[85] **103** (Scheme 29b) or diamines[86] **100** (Scheme 29a) can be utilized to make oxazepanones **105** or diazepanones **102** respectively. An interesting related transformation was reported by Lang and Wang. [87] Enantioselective NHC-catalyzed amination of α-bromoenals **106** with *ortho*-benzodiamines **107** yielded corresponding products of formal [4+3] annulation **108** in high yields with excellent enantioselectivities (Scheme 29c).

Scheme 29



Scheme 30



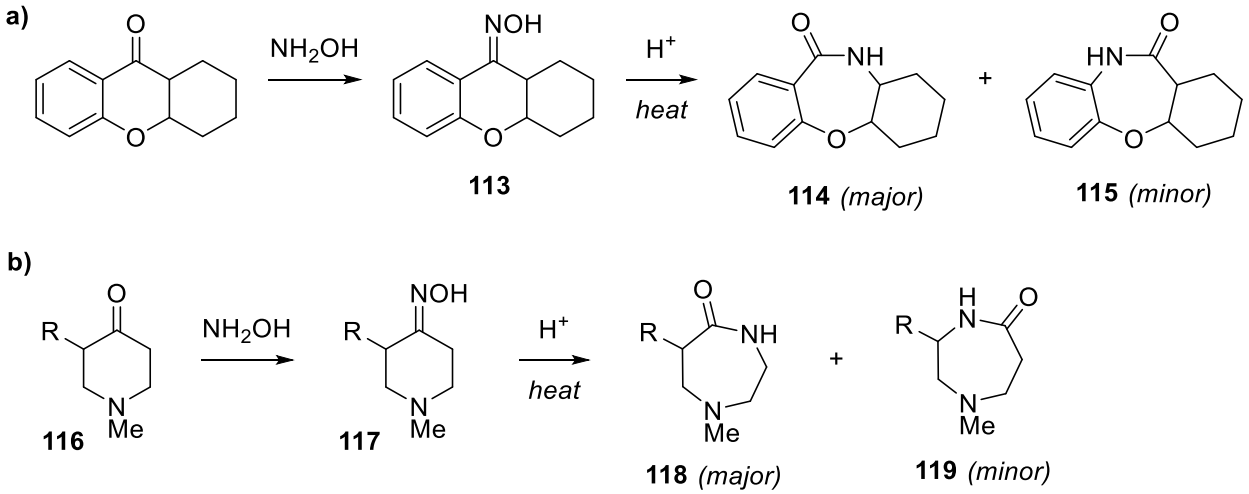
A conceptually interesting way to access regio-isomeric dibenzoxazepanones **111** and **112** from aminoquinoline benzamides **109** and *ortho*-bromophenols **110** was reported by Zhu[88] (Scheme 30). Through the choice of conditions, the reaction can be directed to proceed towards **111** via a sequential C−H etherification and subsequent amide alkylation, both controlled by the aminoquinoline group (removable directing auxiliary) and Cu(I), or in direction of **112** through a C−H etherification followed by Smiles rearrangement promoted by Cu(II) and *t*-BuOK.

1.7 Ring expansion

Historically, methods for lactam synthesis largely relied on ring expansion rearrangements of oximes (Beckmann rearrangement) and adizohydrin intermediates (Schmidt rearrangements) obtained from ketones. Unfortunately, in many cases this inherently elegant transformations require harsh reaction conditions which limit its usefulness to carefully chosen substrates and cause regioselectivity problems.[89]

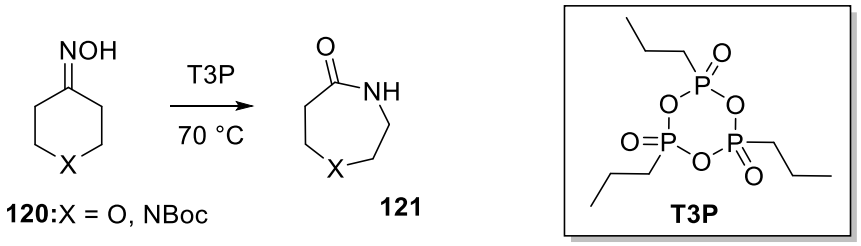
The first reported example of using Beckmann rearrangement in synthesis of oxazepanones was carried out by McEvoy and Allen in 1970 (Scheme 31a).[90] The rearrangement of the oxime **113** furnished a separable mixture of lactams **114** and **115**, in which lactam **114**, the product of aryl migration, prevailed. Similar results were obtained by Moormann[91] for heteroazepanones (Scheme 31b). Various ketones **116** were converted to oximes **117**, and then Beckmann rearrangement produced a 7:3 mixture of isomeric lactams **118** and **119** that were separated using column chromatography.

Scheme 31



In response to these problems, many groups have reported modifications of the reaction that allows the transformation to proceed under milder conditions. For instance, Augustine et al.[Ошибка! Закладка не определена.] reported an efficient catalytic method for the Beckmann rearrangement of ketoximes **120** to amides **121** mediated in excellent yields by a catalytic amount (15 mol %) of propylphosphonic anhydride (T3P) at room temperature (Scheme 32). The main advantages of this environmentally friendly protocol include procedural simplicity, particularly ease of isolation of the products, and remarkable functional group tolerance. Other reagents used to facilitate Beckman rearrangement towards heteroazepanones at mild conditions include $Ca(NTf_2)_2$, [92] cyanuric trichloride,[93] and combination of $InBr_3$ with AgOTf.[94]

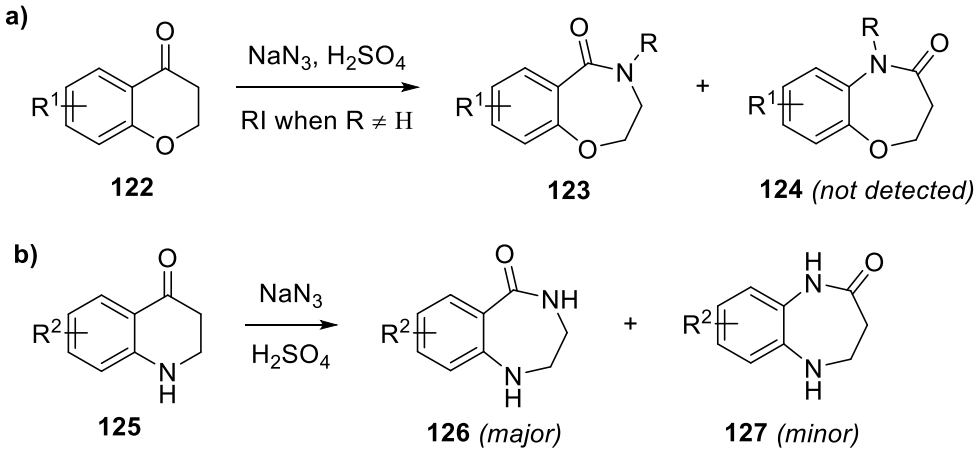
Scheme 32



Early examples of using Schmidt rearrangement in heteroazepanone synthesis include works by Wright[95] and Lindwall[96]. Substituted chromanones **122** were subjected to sodium azide in presence of sulfuric acid and then in some cases treated with alkyl iodides to form corresponding oxazepanones **123** in 24 – 67% yield (Scheme 33a). Schmidt reaction with an unsymmetrical ketone can theoretically lead to two possible products. It is notable that even though in the reaction with 4-chromanone (**122**, R^1 = H) while the yields did not rule out the formation of both possible isomers (**123** and **124**) an alternative benzoxazepanone **124** has not been detected in the reaction mixture. In a similar reaction performed by Skalitzky and co-workers [97] substituted

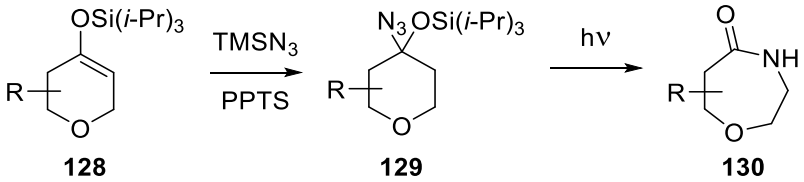
dihydroquinolinones **125** were converted to corresponding diazepanones **126** by means of Schmidt rearrangement (Scheme 33b). The desired transformation was achieved in yields around 85% using sodium azide and methanesulfonic acid. Although the described reaction is quite efficient, the regioselectivity of the rearrangement was reported to be problematic to control. In addition to the desired product **126**, the regioisomeric amide **127** was also formed in ~10% yield.

Scheme 33



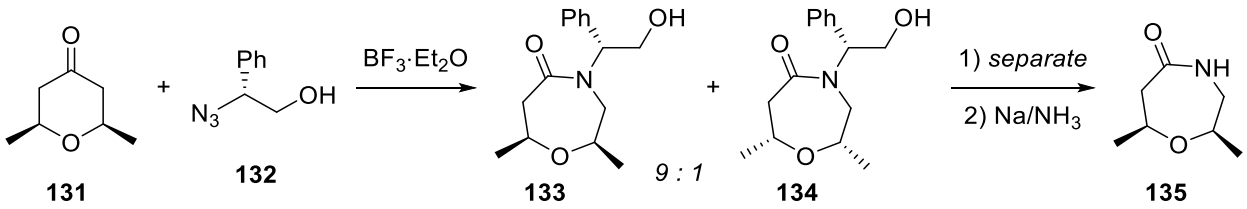
Despite the development of a variety of new protocols of Schmidt rearrangement its utility in many cases is limited by to the severity of the reaction conditions required to effect the ring expansion. Strong protic or Lewis acids are often required, giving rise to the problematic side reactions observed in acid labile molecules. In order to overcome this scope limitations Evans et al. [98] have developed the protocol for a photoinduced Schmidt rearrangement of the azidotriisopropylsilyl ethers **129** (Scheme 34), which are prepared by the direct azidonation of the triisopropylsilyl enol ethers **128**. The reaction was shown to be applicable to heterocyclic starting materials and afforded oxazepanones **130** in yields over 80% at 0 °C in one hour.

Scheme 34



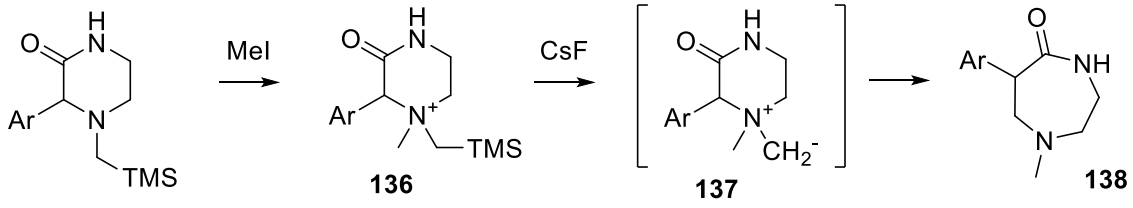
A synthetic route to the enantiopure oxazepanones reported by Aube[99] represents another interesting application of Schmidt rearrangement (Scheme 35). The Lewis acid-mediated azido-Schmidt reaction of chiral azido alcohol **132** with ketone **131** furnished a 9:1 diastereomeric mixture of ring-expanded lactams **133** and **134** in 75% overall yield. These lactams were separated using chromatography, and the major product **133** was subjected to reductive removal of the phenethyl group using metal ammonia to provide the enantiopure product **135**.

Scheme 35



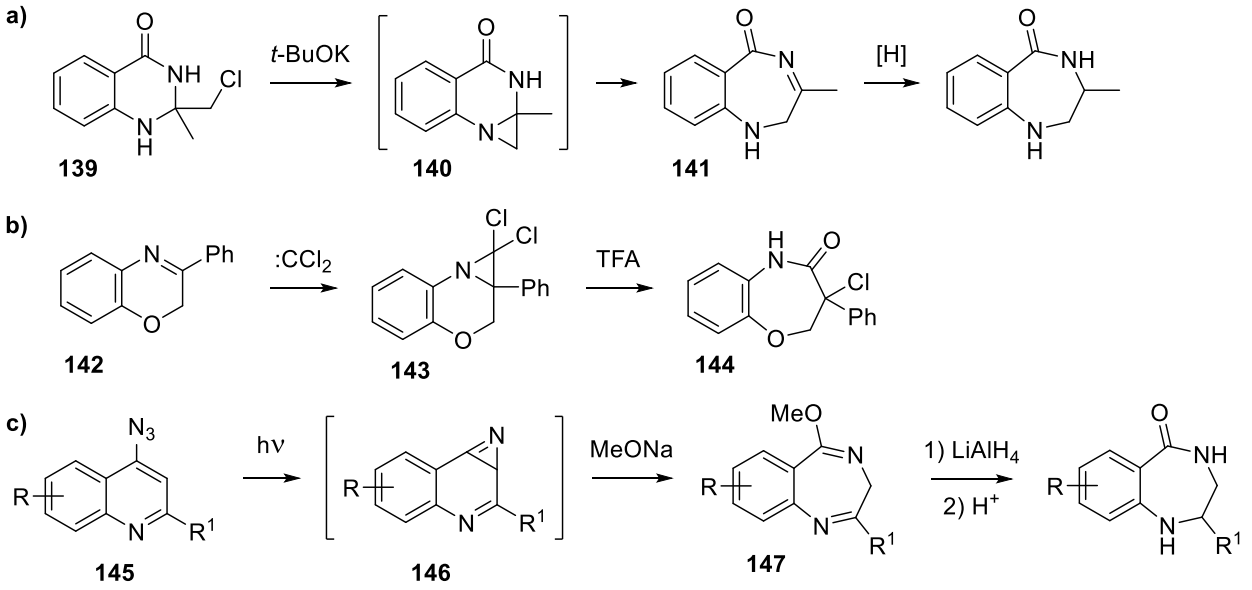
Stevens rearrangement is another example of ring expansion reaction which was used in oxazepanone synthesis.[100] Fluoride ion-induced desilylation of trimethylsilylmethylpiperazinium ions **136** was shown to lead to corresponding methylides **137** which underwent rearrangement to form seven-membered rings **138** (Scheme 36).

Scheme 36



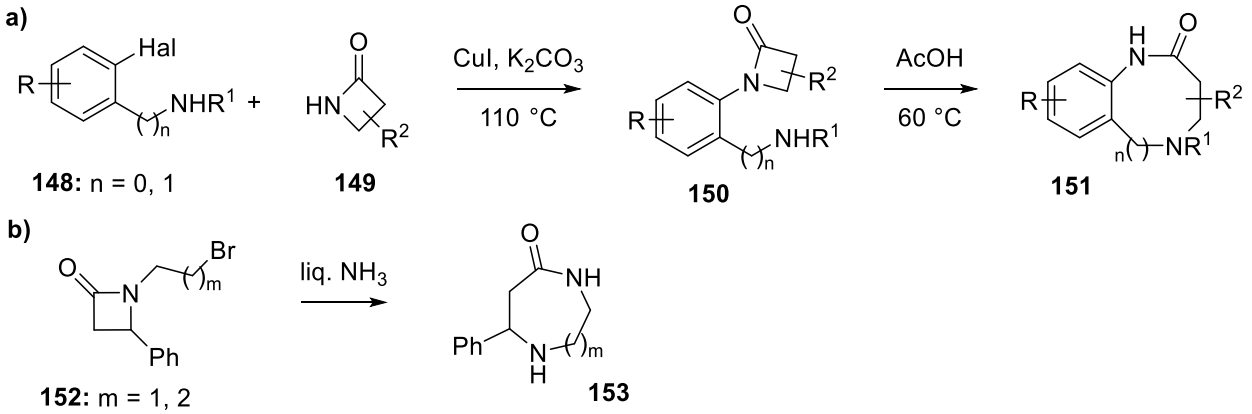
Many reported strategies of heteroazepanone and heteroazocanone synthesis through ring expansion rely on ring opening of azeridines (Scheme 37). For example,[101] treatment of the appropriately substituted dihydroquinazolinones **139** with potassium *tert*-butoxide allowed formation of aziridine intermediates **140** and yielded the benzodiazepanones **141** (Scheme 37a). It was shown that transformation is initiated by anion formation through *N*-deprotonation. The next step was ring closure to aziridine **140**, which then isomerized to the benzodiazepane **141**. In another study,[102] a synthetic sequence consisting of cycloaddition of dichlorocarbene to the C=N double bond of benzoxazin **142** (Scheme 37b), leading to the formation of the gem-dihaloazirino-fused heterocycle **143**, and subsequent aziridine ring opening with N–C bond breaking with trifluoroacetic acid at room temperature was shown to furnish benzoxazepanone **144**. Likewise, irradiation of the azides **145** (Scheme 37c) resulted in ring expansion to yield the desired seven-membered ring **147** via the azirine intermediates **146** as reported by Sashida et al.[103]

Scheme 37



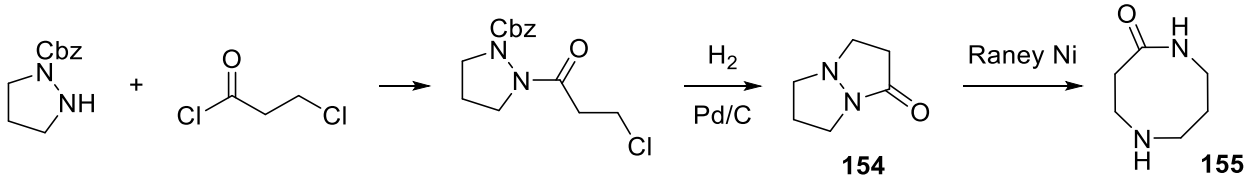
Ring expansion of azetidines was also shown to be a viable strategy for diazepanone and diazocanone synthesis. In the study by Buchwald and co-workers,[104] a simple method for the preparation of medium ring heterocycles **151** employing a Cu-catalyzed coupling of a β-lactams **149** with an aryl bromide or iodide **148** followed by intramolecular attack of a pendant amino group in **150** has been developed (Scheme 38a). A ring-expansion step proceeded through an intramolecular transamidation reaction. Similarly, tethered halides **152** treated with liquid ammonia gave directly the corresponding seven-, eight-, and nine-membered ring-expanded azalactams **153** in good yield as shown by Crombie et al. (Scheme 38b).[105]

Scheme 38



Yet another strategy for diazepanone and diazocanone synthesis relies on ring opening in fused heterocyclic systems. For example, in the work by Sherrill[106] unsubstituted diazocanone **155** was obtained via cleavage of the N-N bond in tetrahydropyrazolopyrazole ring system **154** (Scheme 39) which was accomplished in high yield by catalytic hydrogenation using Raney nickel.

Scheme 39



1.8 Conclusion

Heteroazepanones and heteroazocanones are a structural moieties found in a wide range of natural products, which possess a broad spectrum of biological activities, as well as important building blocks for drugs that have found both clinical and commercial success.

The utility of this heterocyclic substrates along with their importance for medicinal chemistry stimulated the development of many methods for their preparation. Despite the synthetic challenges associated with the cyclization of medium-sized rings, numerous strategies have been developed, including methods based on cyclization and ring expansion reactions, along with multicomponent and tandem methods.

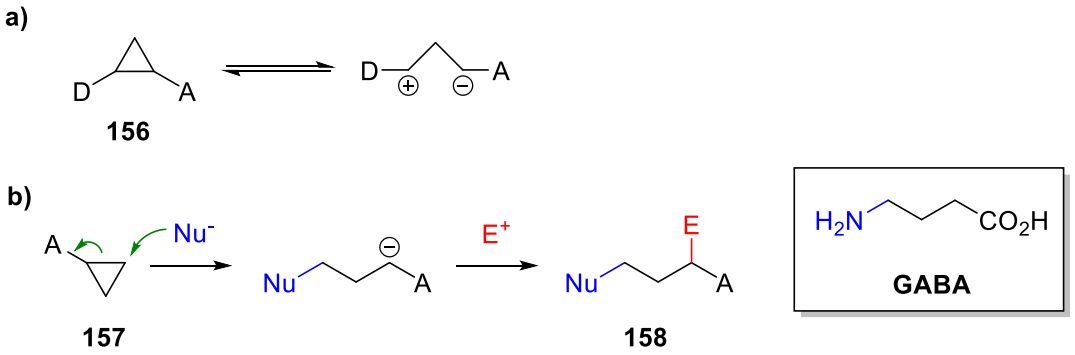
However, there are much fewer approaches for preparing enantiomerically pure heteroazepanones and heteroazocanones. Helping to address this problem we designed methods for the diastereoselective addition of tethered chiral nucleophiles to prochiral cyclopropenes that allow the expedited access to stereodefined cyclopropane-fused oxazepanones and diazepanones (See Chapters 4 and 5).

Chapter 2. Nucleophilic addition of amines to cyclopropenes en route to GABA amides

2.1 Introduction

Cyclopropanes are characterized by enhanced strain energy. This feature allows for the utilization of strain-release driven transformations such as a ring opening. The propensity of donor–acceptor cyclopropanes[145] (DAC) (**156)** toward ring cleavage (Scheme 40a) is proportional to polarization of the C–C bond between electron-donating and electron-withdrawing groups. In our studies[107] of DACs, we investigated the possibility to access substituted GABA derivatives **158** via the ring opening of DAC **157** (Scheme 40b).

Scheme 40



γ-Aminobutyric acid (GABA) is the prominent inhibitory neurotransmitter in the mammalian central nervous system which plays a principal role in reducing neuronal excitability,[108] and is a species of immense importance for modern bioorganic and medicinal chemistry. This motif is omnipresent in natural products, including Bistramide A (Figure 12).[109]

GABA derivatives are also widely used in numerous over-the-counter and prescription

medicinal agents, such as Lyrica (Pregabalin), Noofen (Phenibut), Lioresal (Baclophen), or anti-arthritic drug Trocade (Cipemastat) (Figure 12).

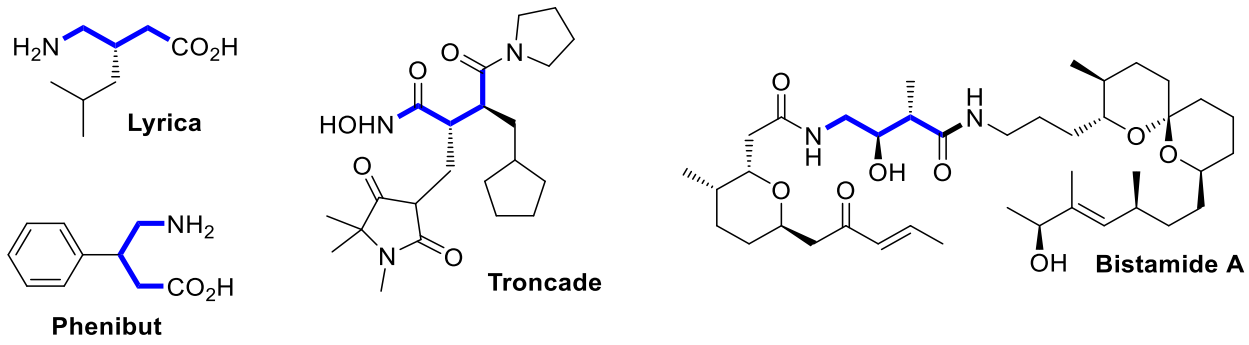
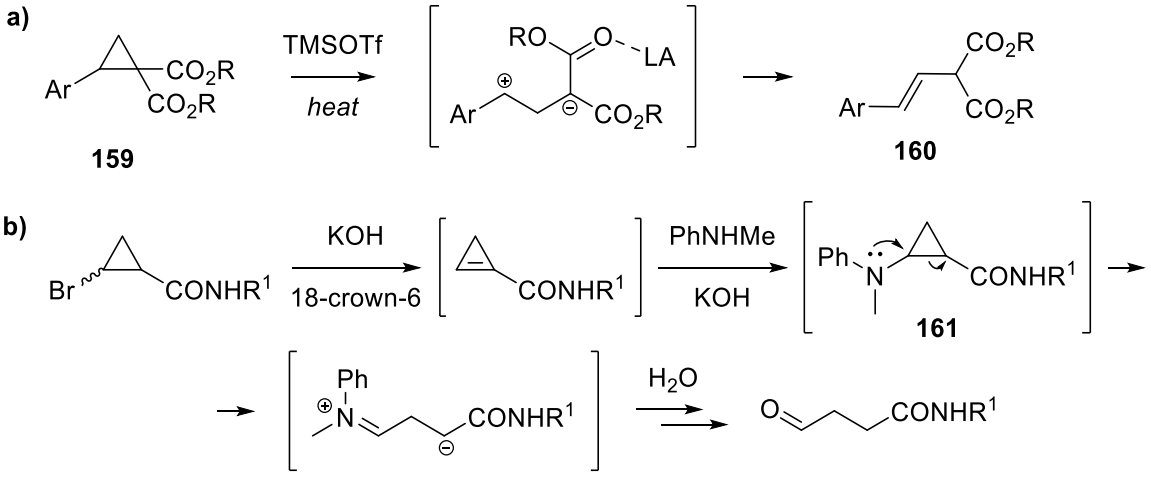


Figure 12. Pharmacologically important GABA derivatives

2.2 Prior attempts of Nucleophilic addition of amines to 3,3-disubstituted cyclopropenes

In order to achieve the polarization required for cyclopropane ring cleavage, strong EWGs are commonly employed. A typical example would be two ester groups (**159**),[110] additionally activated by a Lewis acid ("pull" strategy) (Scheme 41a), which leads to products **160** with an "extra" carboxylate moiety at the α-carbon. The possibility to employ an alternative "push" strategy (Scheme 41b) by taking advantage of our formal nucleophilic substitution methodology that allows for installation of various *N*-moieties in the cyclopropane ring (**161**) was previously proposed in a report from our group.[107] Herein we demonstrate the proof of concept and employment of this strategy toward synthesis of GABA amide derivatives.

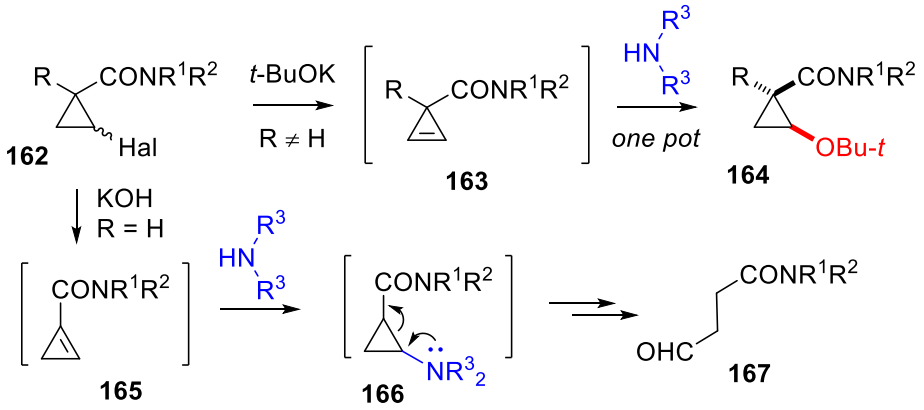
Scheme 41



Formal nucleophilic substitution of halocyclopropanes **162**[107] provides convenient access to various cyclopropylamine derivatives **166**, including carboxamides and sulphonamides of trans-β-aminocyclopropanecarboxylic acid (β-ACC), *N*-cyclopropylhetaryls and *N*-cyclopropylanilines (Scheme 42).[107,111] These reactions proceed via a base-driven nucleophilic addition across the double bond of conjugate cyclopropene **165**.[112,113] However, attempts to isolate hydroamination products resulting from the addition of electron-rich amine derivatives to the in situ generated, very electrophilic 1-substituted cyclopropenes **165** were unsuccessful. Small amount of water generated as by-product upon dehydrohalogenation of **162** in the presence of KOH resulted in a rapid, amine-mediated ring-opening hydration of intermediate cyclopropene **165** affording aldehyde **167** (Scheme 42).[107] Furthermore, nitrogen nucleophiles do not easily add to less electrophilic, non-conjugate 3,3-disubstituted cyclopropenes **163** under conditions used for generation thereof.[114] This reaction was completely suppressed by a much more facile addition of an alkoxide (employed as a base for dehydrohalogenation step), to afford cyclopropanol ether **164**. Thus, employment of stable, isolated cyclopropenes **163**[115] was envisaged as an alternative

approach to hydroamination that could be carried out under alcohol- and/ or water-free conditions.

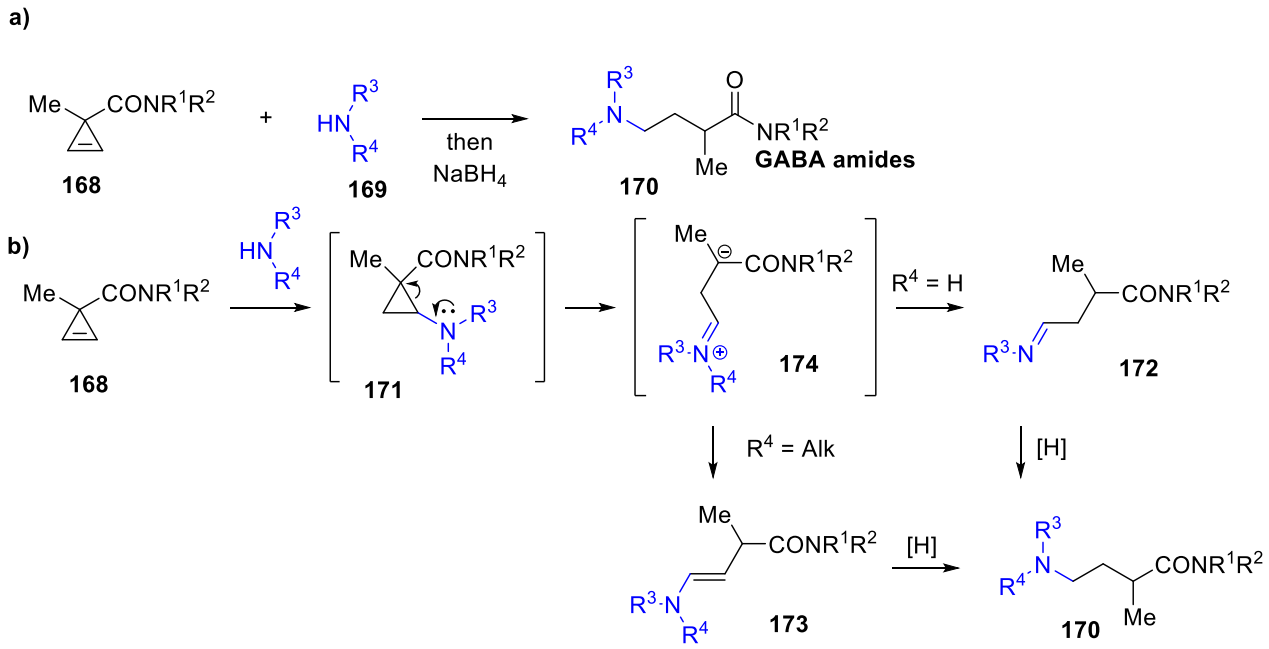
Scheme 42



2.3 Accessing GABA derivatives via the ring opening of donor–acceptor cyclopropanes

Herein, we have successfully employed a “push” strategy for ring opening of “push–pull” cyclopropanes **171** generated in situ via the unassisted nucleophilic addition of electron-rich amines across the double bond of cyclopropene-3-carboxamides **168** (Scheme 43). This concept was utilized in efficient one-pot synthesis of GABA derivatives **170**.

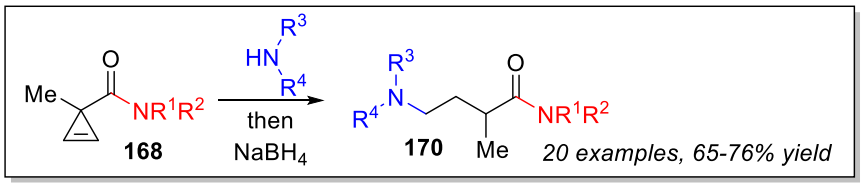
Scheme 43

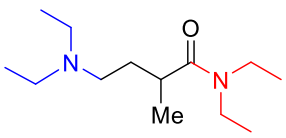


Firstly, we exposed neat *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide (**168a**, $R^1 = R^2 = Et$)[115] to diethylamine (**169a**, $R^4 = R^3 = Et$, 3.0 equiv.) at various temperatures to monitor the ring opening (Scheme 43a). It was found that heating the mixture at 100 °C allowed for complete and clean ring cleavage. The GC analysis of crude reaction mixtures showed a single product peak, attributed to enamine **172aa**. Next, the crude mixture was treated with borohydride ($NaBH_4$ or $NaBH(OAc)_3$) in dichloromethane to afford the target amide **170aa** as a single product in good yield.

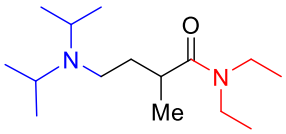
It was anticipated that the addition of an electron-rich amino group would help trigger the desired bond cleavage in an intermediate **171** (Scheme 43b). The resulting zwitterionic intermediate **174**, in the presence of a proton source, would be stabilized in a form of an imine **172** (if derived from primary amine **169**) or an enamine **173**, respectively. Species **172** or **173** can subsequently be reduced in situ to give GABA amide **170**, or be employed in various imine or enamine chemistry.

Scheme 44

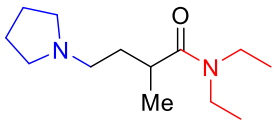




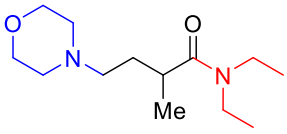
170aa
1 h at 100 °C, **66%**



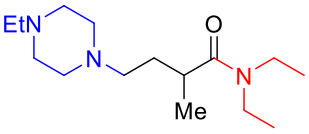
170ab
1 h at 125 °C, **NR**



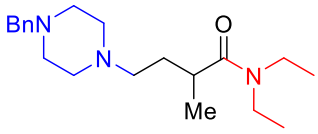
170ac
1 h at 100 °C, **71%**



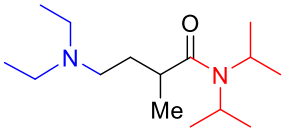
170ad
1 h at 100 °C, **68%**



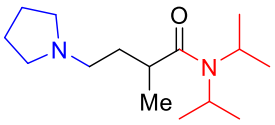
170ae
1 h at 100 °C, **72%**



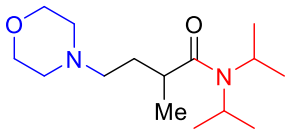
170af
1 h at 100 °C, **75%**



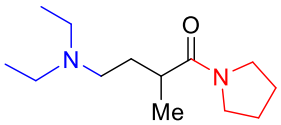
170ba
1 h at 100 °C, **71%**



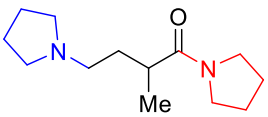
170bc
1 h at 100 °C, **73%**



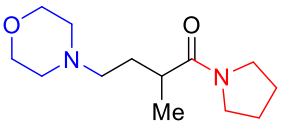
170bd
1.5 h at 100 °C, **66%**



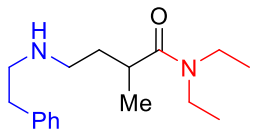
170ca
1 h at 100 °C, **65%**



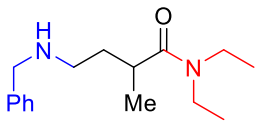
170cc
1 h at 100 °C, **73%**



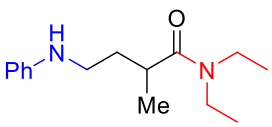
170cd
1 h at 100 °C, **68%**



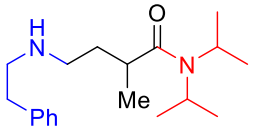
170ag
2 h at 100 °C, **75%**



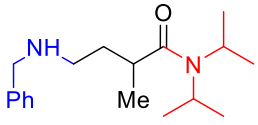
170ah
2 h at 115 °C, **65%**



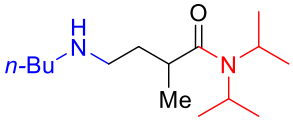
170ai
5 h at 140 °C, **68%**



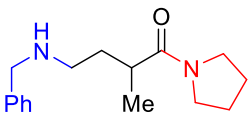
170bg
2 h at 100 °C, **76%**



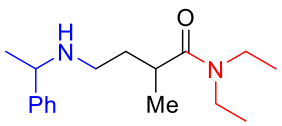
170bh
2 h at 100 °C, **68%**



170bj
1 h at 100 °C, **76%**



170ch
2 h at 100 °C, **65%**



170ak
3 h at 100 °C, **65%** (1:1 dr)

*Reaction times and temperatures for the first stage are provided

Interestingly, under similar conditions, diisopropylamine (**169b**) did not react at all (**170ad** in Scheme 44), leaving cyclopropene **168a** intact even after extended heating at 125 °C. Apparently, this bulky amine was insufficiently nucleophilic to enable the hydroamination step (**170ab**). In contrast, cyclic secondary amines, such as pyrrolidine (**169c**), morpholine (**169d**), and *N*-ethyl- (**169e**), *N*-benzylpiperazines (**169f**) afforded GABA amides **170ad**–**170af** in good yields. *N*,*N*-Diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**168b**) and (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**168c**) proved to be similarly efficient as **168a** with a number of secondary amines. Reaction with primary amines, such as phenethylamine (**169g**), benzylamine (**169h**), and *n*-butylamine (**169j**), also proceeded uneventfully, although somewhat more sluggishly. It was also necessary to raise the temperature to 140 °C to drive the reaction with aniline (**168i**) to complete conversion.

Finally, a possibility to induce a diastereoselective ring cleavage upon the addition of chiral amines was probed (Scheme 44) by reacting cyclopropene **168a** with α-phenylethylamine (**169k**). Unfortunately, transfer of stereochemical information from a remote stereogenic center was not efficient, and the corresponding adduct **170ak** was produced as a 1 : 1 mixture of two diastereomers.

2.4 Conclusion

An efficient one-pot synthesis of various GABA amides has been demonstrated. Unassisted nucleophilic addition of primary and secondary amines across the double bond of cyclopropene-3-carboxamides is followed by a ring opening of the resulting donor-acceptor cyclopropanes. Subsequent in situ reduction of enamine or imine intermediates allows access to substituted GABA derivatives.

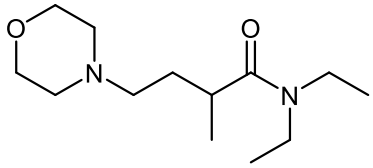
2.5 Experimental

2.5.1 General information

NMR spectra were recorded on a Bruker Avance DRX-500 with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were registered with broadband decoupling. The (+) and (-) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. IR spectra were recorded on a Shimadzu FT-IR 8400S instrument. HRMS was carried out on LCT Premier (Micromass Technologies) instrument; ESI TOF detection techniques were used. GC analyses were performed on a Shimadzu GC-2010 gas chromatograph with FID detector and equipped with an AOC20i auto-injector and an AOC-20S auto-sampler tray (150 vials); 30 m 0.25 mm 0.25 mm capillary column, SHR5XLB, polydimethylsiloxane; 5% Ph was employed. Helium (99.96%), additionally purified by passing consecutively through a CRS oxygen/moisture/hydrocarbon trap (#202839) and VICI oxygen/moisture trap (P100-1), was used as a carrier gas. Hydrogen gas was used as FID fuel; zero-grade air and zerograde nitrogen were used as an oxidant and make-up gas, respectively, for the FID. All these gases were purified by passing through CRS #202839 traps. The following GC parameters were used for all analyses: carrier gas flow rate 2.5 mL/min; oven temperature program: 50 °C (2 min) - 20 °C/min - 230 °C (6 min), injector temperature 275 °C. Column chromatography was carried out on silica gel (Sorbent Technologies, 40-63 μm). Pre-coated silica gel plates (Sorbent Technologies Silica XG 200 μm) were used for TLC analyses. Anhydrous dichloromethane was obtained by passing degassed commercially available HPLC-grade inhibitor-free solvents consecutively through two columns filled with activated alumina and stored over molecular sieves under nitrogen. Water was purified by dual stage deionization followed by dual stage reverse osmosis. Synthesis of starting materials: *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide (**168a**), *N*,*N*-diisopropyl-1-

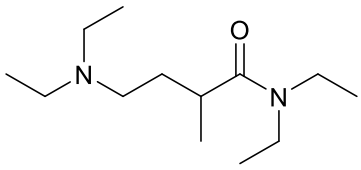
methylcycloprop-2-ene-1-carboxamide (**168b**) and (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**168c**) was detailed in previously published paper from our group.[115] Commercially available amines: aniline (**169i**), diethylamine (**169a**), pyrrolidine (**169c**), morpholine (**169d**), *n*-butylamine (**169j**) were dried with granulated potassium hydroxide and distilled immediately prior to use. All other reagents were purchased from commercial vendors and used as received.

2.5.2 Synthesis of GABA-amide derivatives

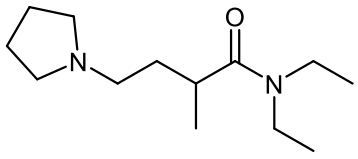


N,N-Diethyl-2-methyl-4-morpholinobutanamide **(170ad)**: Typical procedure: Oven-dried 2 mL Weaton vial was charged with *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide (**168a**) (100 mg, 0.65 mmol, 1.0 equiv) and morpholine (**169d**) (86 μL, 85 mg, 0.96 mmol, 1.5 equiv). The mixture was stirred at 100 °C for 1 h, then $NaBH_4$ (25 mg, 0.65 mmol, 1.0 equiv) in dry dichloromethane (2 mL) was added, and the resulting solution was stirred overnight at r.t. The reaction mixture was partioned between 2M aqueous NaOH (2 mL) and ethyl acetate (2 mL). The organic phase was separated, the aqueous layer was extracted with ethyl acetate (2 x 2 mL). Combined organic layers were concentrated in vacuum and diluted with 2M aqueous HCl (3 mL). The resulting solution was washed with ethyl acetate (3 x 5 mL), then basified with NaOH and extracted with ethyl acetate (3 x 5 mL). Combined organic layers were washed with brine (5 mL), dried with $MgSO_4$ and evaporated. Preparative column chromatography of residue on silica gel doped with 0.5% of triethylamine in EtOAc afforded the titled compound as a yellow oil, R_f 0.25 (EtOAc). Yield 107 mg (0.44 mmol, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (t, *J* = 4.7 Hz, 4H), 3.45–3.27 (m, 4H), 2.76–2.72 (m, 1H), 2.42 (br. s, 2H), 2.36 (br. s, 2H), 2.30–2.24 (m, 2H), 1.92–1.88 (m, 1H), 1.55–1.51 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 67.2 (-, 2C), 56.8 (-), 53.8 (-, 2C), 42.0 (-),

40.4 (-), 33.4 (+), 31.0 (-), 18.6 (+), 15.0 (+), 13.2 (+); FT IR (NaCl, cm^{-1}): 2930, 2854, 2806, 1659, 1643, 1614, 1445, 1427, 1379, 1359, 1257, 1116, 1070, 995, 854, 793, 773; HRMS (TOF ES): found 265.1880, calculated for $C_{13}H_{26}N_2O_2Na$ (M+Na) 265.1892 (4.5 ppm).

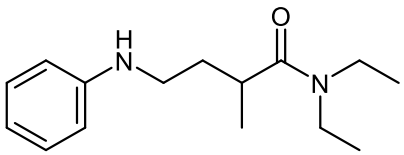


4-(Diethylamino)-N,N-diethyl-2-methylbutanamide (**170aa**): Was prepared according to Typical Procedure, *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(168a)** (100 mg, 0.65 mmol, 1.0 equiv) and diethylamine (**169a**) (202 μL, 143 mg, 1.95 mmol, 3.0 equiv). The reaction was carried out at 100 °C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.28 (DCM/MeOH 10:1). Yield 98 mg (0.43 mmol, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.44–3.36 (m, 2H), 3.31–3.20 (m, 2H), 2.71–2.64 (m, 1H), 2.54–2.43 (m, 4H), 2.43–2.32 (m, 2H), 1.85–1.81 (m, 1H), 1.50–1.46 (m, 1H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 50.5 (-), 46.7 (-, 2C), 41.9 (-), 40.4 (-), 33.5 (+), 31.3 (-), 18.4 (+), 15.0 (+), 13.2 (+), 11.7 (+, 2C); FT IR (NaCl, cm^{-1}): 2968, 2932, 2799,1637, 1448, 1429, 1379, 1261, 1126, 1070; HRMS (TOF ES): found 251.2095, calculated for $C_{13}H_{28}N_2ONa$ (M+Na) 251.2099 (1.6 ppm).

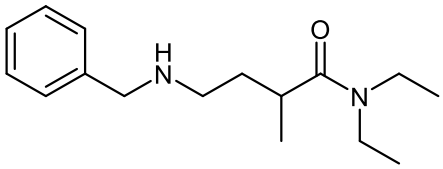


N,N-Diethyl-2-methyl-4-(pyrrolidin-1-yl)butanamide (**170ac**): Was prepared according to Typical Procedure, *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(168a)** (100 mg, 0.65 mmol, 1.0 equiv) and pyrrolidine (**169c**) (160 μL, 139 mg, 1.95 mmol, 3.0 equiv). The reaction was carried out at 100 °C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative

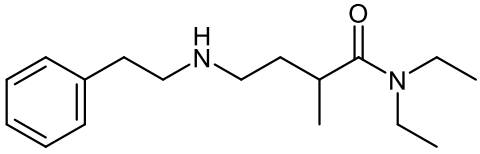
column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.30 (DCM/MeOH 10:1). Yield 104 mg (0.46 mmol, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.42–3.36 (m, 2H), 3.34–3.23 (m, 3H), 2.76–2.71 (m, 1H), 2.50–2.44 (m, 4H), 2.37–2.34 (m, 1H), 1.92–1.88 (m, 1H), 1.74 (br. s, 4H), 1.61–1.57 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.11–1.07 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 54.1 (-), 54.1 (-, 2C), 41.9 (-), 40.4 (-), 33.8 (+), 33.3 (-), 23.6 (-, 2C), 18.4 (+), 15.0 (+), 13.2 (+); FT IR (NaCl, cm^{-1}): 2968, 1786, 1634, 1464, 1433, 1379, 1261, 1221, 1128, 1097, 752, 733; HRMS (TOF ES): found 227.2117, calculated for $C_{13}H_{27}NO_2$ (M+H) 227.2123 (2.6 ppm).



N,N-Diethyl-2-methyl-4-(phenylamino)butanamide (**170ai**): Was prepared according to Typical Procedure, *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(168a)** (100 mg, 0.65 mmol, 1.0 equiv) and aniline (**169i**) (118 μL, 121 mg, 1.30 mmol, 2.0 equiv). The reaction was carried out at 140 °C for 5 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.30 (DCM/MeOH 15:1). Yield 110 mg (0.44 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.5 Hz, 2H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 7.9 Hz, 2H), 3.74 (br. s, 1H), 3.42–3.34 (m, 2H), 3.32–3.24 (m, 2H), 3.15–3.04 (m, 2H), 2.83–2.74 (m, 1H), 2.17–2.04 (m, 1H), 1.71–1.63 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.14–1.09 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 148.4, 129.2 (+, 2C), 117.2 (+), 112.7 (+, 2C), 42.4 (-), 41.9 (-), 40.5 (-), 33.9 (+), 33.9 (-), 18.6 (+), 14.9 (+), 13.2 (+); FT IR (NaCl, cm^{-1}): 3350, 2972, 1932, 1628, 1603, 1508, 1466, 1433, 1321, 1260, 750, 733, 694; HRMS (TOF ES): found 271.1773, calculated for $C_{15}H_{24}N_2ONa$ (M+Na) 271.1786 (4.8 ppm).

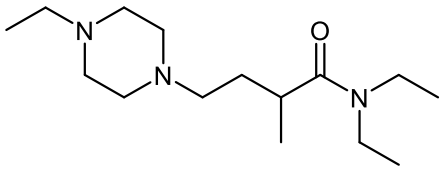


4-(Benzylamino)-N,N-diethyl-2-methylbutanamide (**170ah**): Was prepared according to Typical Procedure, *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(168a)** (100 mg, 0.65 mmol, 1.0 equiv) and benzylamine (**169h**) (142 μL, 139 mg, 1.30 mmol, 2.0 equiv). The reaction was carried out at 115 ^{o}C for 2 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.33 (DCM/MeOH 10:1). Yield 111 mg (0.42 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.17 (m, 5H), 3.76–3.69 (m, 2H), 3.36–3.24 (m, 4H), 2.80–2.71 (m, 1H), 2.64–2.52 (m, 2H), 2.47 (br. s, 1H), 1.93–1.85 (m, 1H), 1.59–1.51 (m, 1H), 1.12 (t, *J* = 7.1 Hz, 3H), 1.06–1.01 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 139.9, 128.5 (+, 2C), 128.4 (+, 2C), 127.1 (+), 54.0 (-), 47.2 (-), 42.0 (-), 40.5 (-), 34.4 (-), 33.6 (+), 18.4 (+), 15.0 (+), 13.2 (+); FT IR (NaCl, cm^{-1}): 3282, 2972, 2931, 1634, 1454, 1433, 1379, 1263, 1219, 1125, 1097, 733, 698; HRMS (TOF ES): found 285.1933, calculated for $C_{16}H_{26}N_2ONa$ (M+Na) 285.1943 (3.5 ppm).

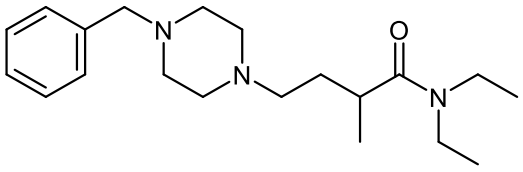


N,N-Diethyl-2-methyl-4-(phenethylamino)butanamide **(170ag)**: Was prepared according to Typical Procedure, *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(168a)** (100 mg, 0.65 mmol, 1.0 equiv) and phenethylamine (**169g**) (123 μL, 118 mg, 0.98 mmol, 1.5 equiv). The reaction was carried out at 100 ^{o}C for 2 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.32 (DCM/MeOH 15:1). Yield 135 mg (0.49 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.7 Hz, 2H), 7.20–7.18 (m, 3H), 3.41–3.20 (m, 4H), 2.88

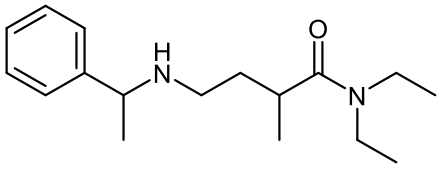
(t, *J* = 6.1 Hz, 2H), 2.84–2.81 (m, 2H), 2.78 (br.s, 1H), 2.78–2.69 (m, 1H), 2.69–2.57 (m, 2H), 1.92–1.83 (m, 1H), 1.64 - 1.55 (m, 1H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 139.8, 128.8 (+, 2C), 128.6 (+, 2C), 126.3 (+), 51.0 (-), 47.4 (-), 42.0 (-), 40.5 (-), 36.1 (-), 34.1 (-), 33.6 (+), 18.3 (+), 15.0 (+), 13.2 (+); FT IR (NaCl, cm^{-1}): 3303, 2970, 2932, 1632, 1452, 1433, 1379, 1261, 924, 910, 738, 700; HRMS (TOF ES): found 277.2275, calculated for $C_{17}H_{29}N_2O$ (M+H) 277.2280 (1.8 ppm).



N,N-Diethyl-4-(4-ethylpiperazin-1-yl)-2-methylbutanamide (**170ae**): Was prepared according to Typical Procedure, *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(168a)** (100 mg, 0.65 mmol, 1.0 equiv) and 1-ethylpiperazine (**169e**) (124 μL, 111 mg, 0.98 mmol, 1.5 equiv). The reaction was carried out at 100 °C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.25 (DCM/MeOH 15:1). Yield 126 mg (0.47 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48–3.35 (m, 2H), 3.33–3.19 (m, 2H), 2.71 (td, *J* = 13.7, 6.8 Hz, 1H), 2.37 (br. s, 8H), 2.38 (q, *J* = 7.1 Hz, 2H), 2.29–2.16 (m, 2H), 1.87 (td, *J* = 13.6, 8.0 Hz, 1H), 1.52 (td, *J* = 13.3, 7.3 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.10–1.04 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 56.3 (-, 2C), 53.2 (-), 53.0 (-), 52.4 (-, 2C), 42.0 (-), 40.5 (-), 33.6 (+), 31.6 (-), 18.6 (+), 15.0 (+), 13.3 (+), 12.0 (+); FT IR (NaCl, cm^{-1}): 2968, 2932, 2808, 1643, 1634, 1467, 1447, 1431, 1259, 1164, 1132, 1026, 943, 781; HRMS (TOF ES): found 270.2535, calculated for $C_{15}H_{32}N_3O$ (M+H) 270.2545 (3.7 ppm).

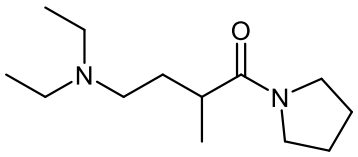


4-(4-Benzylpiperazin-1-yl)-N,N-diethyl-2-methylbutanamide (**170af**): Was prepared according to Typical Procedure, *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(168a)** (100 mg, 0.65 mmol, 1.0 equiv) and 1-benzylpiperazine (**169f**) (169 μL, 172 mg, 0.98 mmol, 1.5 equiv). The reaction was carried out at 100 ºC for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.33 (DCM/MeOH 12:1). Yield 159 mg (0.48 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.19 (m, 5H), 3.46 (s, 2H), 3.52–3.36 (m, 2H), 3.34–3.20 (m, 2H), 2.76–2.68 (m, 1H), 2.45 (br. s, 8H), 2.35–2.22 (m, 2H), 1.88 (td, *J* = 13.6, 7.9 Hz, 1H), 1.53 (td, *J* = 13.4, 7.1 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.11–1.07 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 138.2, 129.3 (+, 2C), 128.3 (+, 2C), 127.2 (+), 63.2 (-), 56.3 (-, 2C), 53.2 (-), 53.1 (-, 2C), 42.0 (-), 40.5 (-), 33.7 (+), 31.4 (-), 18.6 (+), 15.1 (+), 13.3 (+); FT IR (NaCl, cm^{-1}): 2969, 2934, 2808, 1632, 1452, 1433, 1379, 1363, 1346, 1136, 1013, 924, 910, 733, 698; HRMS (TOF ES): found 332.2689, calculated for $C_{20}H_{34}N_3O$ (M+H) 332.2702 (3.9 ppm).

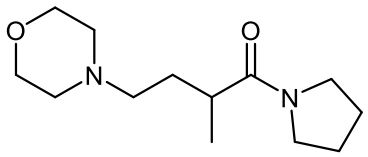


N,N-Diethyl-2-methyl-4-((1-phenylethyl)amino)butanamide (**170ak**): Was prepared according to Typical Procedure, *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(168a)** (100 mg, 0.65 mmol, 1.0 equiv) and 1-phenylethylamine (**169k**) (126 μL, 118 mg, 0.98 mmol, 1.5 equiv). The reaction was carried out at 100 ºC for 3 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.27 (DCM/MeOH

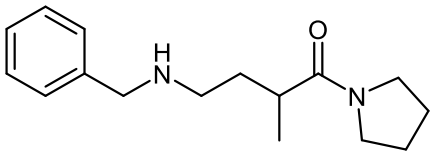
15:1). Yield 117 mg (0.42 mmol, 65%), dr 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br. s, 2H), 7.53 (t, *J* = 6.3 Hz, 4H), 7.39–7.31 (m, 6H), 4.18–4.12 (m, 2H), 3.39–3.18 (m, 8H), 2.88–2.83 (m, 1H), 2.82–2.72 (m, 3H), 2.66–2.58 (m, 2H), 2.08–1.91 (m, 4H), 1.76 (t, *J* = 7.2 Hz, 6H), 1.10 (t, *J* = 7.0 Hz, 6H), 1.03–0.98 (m, 3H), 1.00 (t, *J* = 5.8 Hz, 6H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 175.1, 137.4, 137.2, 129.2 (+, 2C), 129.2 (+, 2C), 129.1 (+), 129.0 (+), 127.9 (+, 2C), 127.9 (+, 2C), 58.6 (+), 58.5 (+), 43.4 (-), 42.8 (-), 42.4 (-), 42.2 (-), 40.7 (-), 40.5 (-), 34.0 (-), 33.7 (-), 29.9 (+), 29.7 (+), 21.1 (+), 20.7 (+), 17.8 (+), 17.4 (+), 14.9 (+, 2C), 13.0 (+, 2C); FT IR (NaCl, cm^{-1}): 3437, 2972, 2749, 1624, 1456, 1382, 1264, 1218, 1078, 768, 703; HRMS (TOF ES): found 277.2269, calculated for $C_{17}H_{29}N_2O$ (M+H) 277.280 (4.0 ppm).



4-(Diethylamino)-2-methyl-1-(pyrrolidin-1-yl)butan-1-one (**170ca**): Was prepared according to Typical Procedure, (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone **(168c)** (100 mg, 0.66 mmol, 1.0 equiv) and diethylamine (**169a**) (205 μL, 145 mg, 1.98 mmol, 3.0 equiv). The reaction was carried out at 100 ^{o}C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.27 (DCM/MeOH 10:1). Yield 97 mg (0.43 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55–3.49 (m, 1H), 3.45–3.39 (m, 3H), 3.06 (q, *J* = 7.1 Hz, 4H), 2.99–2.89 (m, 2H), 2.72–2.63 (m, 1H), 2.18–2.09 (m, 1H), 2.02–1.92 (m, 2H), 1.89–1.83 (m, 3H), 1.38 (t, *J* = 7.2 Hz, 6H), 1.17 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 49.3 (-), 46.6 (-), 46.6 (-, br., 2C), 46.1 (-), 36.1 (+), 26.9 (-), 26.2 (-), 24.3 (-), 17.8 (+), 8.9 (+, 2C); FT IR (NaCl, cm^{-1}): 3422, 2971, 1620, 1468, 1443, 1344, 1271, 1040, 733, 701; HRMS (TOF ES): found 249.1941, calculated for $C_{13}H_{26}NO_2Na$ (M+Na) 249.1943 (0.8 ppm).

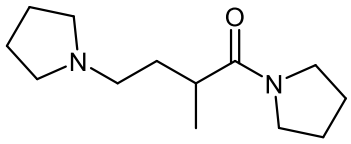


2-Methyl-4-morpholino-1-(pyrrolidin-1-yl)butan-1-one (**170cd**): Was prepared according to Typical Procedure, (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**168c**) (100 mg, 0.66 mmol, 1.0 equiv) and morpholine (**169d**) (86 μL, 86 mg, 0.99 mmol, 1.5 equiv). The reaction was carried out at 100 ^{o}C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.26 (DCM/MeOH 20:1). Yield 108 mg (0.45 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (t, *J* = 4.5 Hz, 4H), 3.59–3.54 (m, 1H), 3.45–3.38 (m, 3H), 2.66–2.57 (m, 1H), 2.42–2.35 (m, 4H), 2.33–2.23 (m, 2H), 1.94–1.88 (m, 3H), 1.86–1.79 (m, 2H), 1.55–1.47 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 67.2 (-, 2C), 57.0 (-), 53.8 (-, 2C), 46.6 (-), 45.8 (-), 36.1 (+), 30.8 (-), 26.3 (-), 24.5 (-), 17.9 (+); FT IR (NaCl, cm^{-1}): 2968, 2870, 1625, 1468, 1441, 1341, 1273, 1117, 1071, 916, 867, 753, 703, 664; HRMS (TOF ES): found 257.2586, calculated for $C_{13}H_{25}N_2O_2$ (M+H) 241.1916 (0.0 ppm).

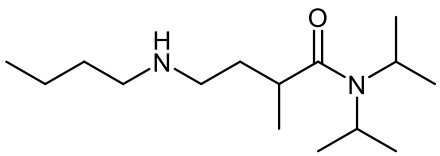


4-(Benzylamino)-2-methyl-1-(pyrrolidin-1-yl)butan-1-one (**170ch**): Was prepared according to Typical Procedure, (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**168c**) (100 mg, 0.66 mmol, 1.0 equiv) and benzylamine (**169h**) (94 μL, 92 mg, 0.86 mmol, 1.3 equiv). The reaction was carried out at 100 ^{o}C for 2 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.30 (DCM/MeOH 15:1). Yield 112 mg (0.43 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (m, 4H), 7.20–7.16 (m, 1H), 3.76 (q, *J* = 13.2 Hz, 2H), 3.46–3.40 (m, 1H), 3.36–3.30 (m, 3H), 3.21 (br. s, 1H), 2.65–2.61 (m, 3H), 1.90–1.82 (m, 3H), 1.78–1.71 (m, 2H),

1.67–1.58 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 138.2, 128.7 (+, 2C), 128.7 (+, 2C), 127.6 (+), 53.4 (-), 46.7 (-), 46.5 (-), 46.0 (-), 36.1 (+), 33.0 (-), 26.3 (-), 24.4 (-), 17.4 (+); FT IR (NaCl, cm^{-1}): 3426, 2966, 2928, 2872, 1628, 1454, 1435, 1340, 743, 700; HRMS (TOF ES): found 261.1960, calculated for $C_{16}H_{25}N_2O$ (M+H) 261.1967 (2.7 ppm).

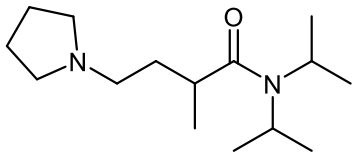


2-Methyl-1,4-di(pyrrolidin-1-yl)butan-1-one (**170cc**): Was prepared according to Typical Procedure, (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone **(168c)** (100 mg, 0.66 mmol, 1.0 equiv) and pyrrolidine (**169c**) (163 μL, 141 mg, 1.98 mmol, 3.0 equiv). The reaction was carried out at 100 ^{o}C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.33 (DCM/MeOH 10:1). Yield 108 mg (0.48 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55–3.50 (m, 1H), 3.44–3.36 (m, 3H), 2.63–3.58 (m, 1H), 2.45 (br. s, 4H), 2.41–2.33 (m, 2H), 1.92–1.87 (m, 3H), 1.84–1.77 (m, 2H), 1.72 (br. s, 4H), 1.60–1.51 (m, 1H), 1.09 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 54.2 (-), 54.1 (-, 2C), 46.5 (-), 45.7 (-), 36.2 (+), 33.1 (-), 26.3 (-), 24.5 (-), 23.6 (-, 2C), 17.6 (+); FT IR (NaCl, cm^{-1}): 2968, 2874, 2791, 1626, 1618, 1460, 1431, 1340, 2968, 2932, 2799,1637, 1448, 1429, 1379, 1261, 1126; HRMS (TOF ES): found 225.1962, calculated for $C_{13}H_{25}N_2O$ (M+H) 225.1967 (2.2 ppm).



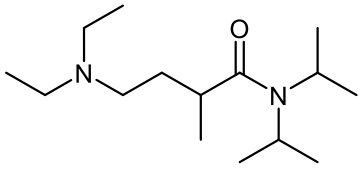
4-(Butylamino)-N,N-diisopropyl-2-methylbutanamide (**170bj**): Was prepared according to Typical Procedure, N,N-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide **(168b)** (100 mg, 0.55 mmol, 1.0 equiv) and butylamine (**169j**) (164 μL, 121 mg, 1.65 mmol, 3.0 equiv).

The reaction was carried out at 100 °C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.28 (DCM/MeOH 10:1). Yield 108 mg (0.42 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (br. s, 1H), 3.46 (br. s, 1H), 2.71–2.63 (m, 1H), 2.57–2.46 (m, 4H), 2.02 (br. s, 1H), 1.84 (td, *J* = 14.1, 7.5 Hz, 1H), 1.49 (dt, *J* = 13.3, 6.7 Hz, 1H), 1.40 (dt, *J* = 14.6, 7.2 Hz, 2H), 1.31–1.22 (m, 8H), 1.17–1.14 (t, *J* = 5.4 Hz, 6H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 49.7 (-), 47.9 (-), 47.9 (+, br.), 45.7 (+), 35.1 (+), 34.5 (-), 32.2 (-), 21.4 (+, br., 2C), 20.8 (+), 20.7 (+), 20.5 (-), 18.2 (+), 14.0 (+); FT IR (NaCl, cm^{-1}): 2962, 2930, 1631, 1466, 1441, 1371, 1303, 1213, 1134, 1040, 754; HRMS (TOF ES): found 257.2581, calculated for $C_{15}H_{32}N_2O$ (M+H) 255.2593 (4.7 ppm).

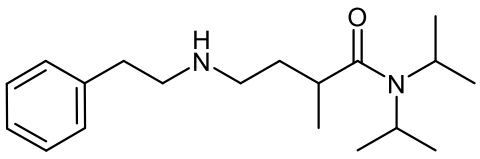


N,N-Diisopropyl-2-methyl-4-(pyrrolidin-1-yl)butanamide (**170bc**): Was prepared according to Typical Procedure, *N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**168b**) (100 mg, 0.55 mmol, 1.0 equiv) and butylamine (**169c**) (136 μL, 118 mg, 1.65 mmol, 3.0 equiv). The reaction was carried out at 100 °C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.31 (DCM/MeOH 15:1). Yield 102 mg (0.40 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (br. s, 1H), 3.44 (br. s, 1H), 2.67 (dt, *J* = 13.5, 6.7 Hz, 1H), 2.47–2.37 (m, 5H), 2.35–2.28 (m, 1H), 1.85 (dt, *J* = 17.1, 6.7 Hz, 1H), 1.69 (s, 4H), 1.50 (td, *J* = 14.1, 6.3 Hz, 1H), 1.29 (d, *J* = 6.2 Hz, 6H), 1.15–1.13 (m, 6H), 1.03 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 54.1 (-), 54.1 (-, 2C), 47.9 (+, br.), 45.6 (+), 35.1 (+), 33.2 (-), 23.5 (-, 2C), 21.4 (+), 21.3 (+), 20.8 (+), 20.8

(+), 18.2 (+); FT IR (NaCl, cm^{-1}): 2964, 2787, 1633, 1464, 1440, 1370, 1211, 1136, 1040, 752; HRMS (TOF ES): found 255.2435, calculated for $C_{15}H_{31}N_2O$ (M+H) 255.2436 (0.4 ppm).

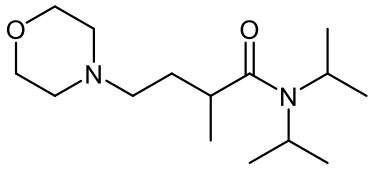


4-(Diethylamino)-N,N-diisopropyl-2-methylbutanamide (**170ba**): Was prepared according to Typical Procedure, *N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**168b**) (100 mg, 0.55 mmol, 1.0 equiv) and diethylamine (**169a**) (171 μL, 121 mg, 1.65 mmol, 3.0 equiv). The reaction was carried out at 100 °C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.26 (DCM/MeOH 10:1). Yield 100 mg (0.39 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06–3.98 (br. m, 1H), 3.45 (br. s, 1H), 2.66 (dt, *J* = 13.5, 6.7 Hz, 1H), 2.57 (q, *J* = 7.0 Hz, 4H), 2.46 (t, *J* = 7.4 Hz, 2H), 1.88 (td, *J* = 14.6, 7.5 Hz, 1H), 1.49 (td, *J* = 13.4, 7.1 Hz, 1H), 1.33 (d, *J* = 6.6 Hz, 6H), 1.17 (t, *J* = 5.9 Hz, 6H), 1.07–1.02 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 50.3 (-), 47.9 (+, br.), 46.8 (-, 2C), 45.7 (+), 35.0 (+), 30.4 (-), 21.4 (+, br., 2C), 20.8 (+), 20.8 (+), 18.2 (+), 11.4 (+, 2C); FT IR (NaCl, cm^{-1}): 2967, 2932, 1636, 1630, 1466, 1439, 1372, 1211, 1134, 1038, 755; HRMS (TOF ES): found 257.2586, calculated for $C_{15}H_{33}N_2O$ (M+H) 257.2593 (2.7 ppm).



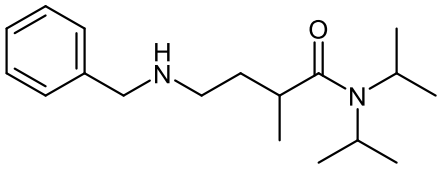
N,N-Diisopropyl-2-methyl-4-(phenethylamino)butanamide (**170bg**): Was prepared according to Typical Procedure, *N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**168b**) (100 mg, 0.55 mmol, 1.0 equiv) and phenethylamine (**169g**) (104 μL, 100 mg, 0.83 mmol, 1.5 equiv). The reaction was carried out at 100 °C for 2 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column

chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.35 (DCM/MeOH 15:1). Yield 100 mg (0.39 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.8 Hz, 2H), 7.22–7.16 (m, 3H), 4.03 (br. s, 1H), 3.50 (br. s, 1H), 2.87–2.84 (m, 2H), 2.80–2.76 (m, 2H), 2.74–2.65 (m, 1H), 2.63–2.53 (m, 2H), 1.86 (td, *J* = 13.9, 7.5 Hz, 1H), 1.62 (br. s, 1H), 1.52 (dt, *J* = 13.5, 6.5 Hz, 1H), 1.36–1.33 (m, 6H), 1.21–1.16 (m, 6H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 140.2, 128.8 (+, 2C), 128.6 (+, 2C), 126.2 (+), 51.3 (-), 47.9 (+, br.), 47.8 (-), 45.8 (+), 36.5 (-), 35.0 (+), 34.6 (-), 21.5 (+, br., 2C), 20.9 (+), 20.8 (+), 18.3 (+); FT IR (NaCl, cm^{-1}): 2967, 1629, 1629, 1372, 1213, 1121, 1040, 755, 701; HRMS (TOF ES): found 305.2595, calculated for $C_{19}H_{33}N_2O$ (M+H) 305.2593 (0.7 ppm).



N,N-Diisopropyl-2-methyl-4-morpholinobutanamide (**170bd**): Was prepared according to Typical Procedure, *N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**168b**) (100 mg, 0.55 mmol, 1.0 equiv) and morpholine (**169d**) (71 μL, 72 mg, 0.83 mmol, 1.5 equiv). The reaction was carried out at 100 °C for 1.5 hours. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.28 (DCM/MeOH 20:1). Yield 98 mg (0.36 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (br. s, 1H), 3.66 (t, *J* = 4.2 Hz, 4H), 3.48 (br. s, 1H), 2.74–2.66 (m, 1H), 2.44–2.41 (br. m, 2H), 2.36–2.31 (br. m, 2H), 2.31–2.21 (m, 2H), 1.89 (td, *J* = 13.5, 7.6 Hz, 1H), 1.48 (td, *J* = 13.4, 6.8 Hz, 1H), 1.33 (t, *J* = 4.3 Hz, 6H), 1.20–1.18 (m, 6H), 1.06 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 67.1 (-, 2C), 56.8 (-), 53.8 (-, 2C), 47.9 (+, br.), 45.7 (+), 34.8 (+), 30.9 (-), 21.4 (+, br., 2C), 20.9 (+), 20.9 (+), 18.5 (+); FT IR (NaCl, cm^{-1}): 2965, 2855, 2807, 1638, 1629,

1462, 1441, 1371, 1305, 1273, 1119, 1038, 916, 866, 752; HRMS (TOF ES): found 271.2391, calculated for $C_{15}H_{31}N_2O_2$ (M+H) 271.2386 (1.8 ppm).



4-(Benzylamino)-N,N-diisopropyl-2-methylbutanamide (**170bh**): Was prepared according to Typical Procedure, *N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**168b**) (100 mg, 0.55 mmol, 1.0 equiv) and benzylamine (**169h**) (78 μL, 77 mg, 0.72 mmol, 1.3 equiv). The reaction was carried out at 100 °C for 2 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on silica gel afforded the title compound as a yellow oil, R_f 0.30 (DCM/MeOH 15:1). Yield 109 mg (0.38 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.26 (m, 4H), 7.24–7.17 (m, 1H), 4.03 (br. s, 1H), 3.73 (s, 2H), 3.46 (br. s, 1H), 2.77–2.68 (m, 1H), 2.64–2.52 (m, 2H), 1.91 (dt, *J* = 14.2, 7.4 Hz, 1H), 1.84 (br.s, 1H), 1.52 (td, *J* = 13.3, 6.6 Hz, 1H), 1.33–1.28 (m, 6H), 1.18–1.14 (m, 6H), 1.05 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 140.3, 128.4 (+, 2C), 128.2 (+, 2C), 126.9 (+), 53.99 (-), 47.8 (+, br.), 47.31 (-), 45.7 (+), 34.9 (+), 34.5 (-), 21.3 (+, br., 2C), 20.8 (+), 20.7 (+), 18.3 (+); FT IR (NaCl, cm^{-1}): 2965, 2930, 2872, 1634, 1439, 1370, 1327, 1304, 1211, 1119, 1040, 737, 698; HRMS (TOF ES): found 291.2430, calculated for $C_{18}H_{31}N_2O$ (M+H) 291.2436 (2.1 ppm).

Chapter 3. Intramolecular nucleophilic addition of stabilized benzylic anions to cyclopropenes

3.1 Introduction

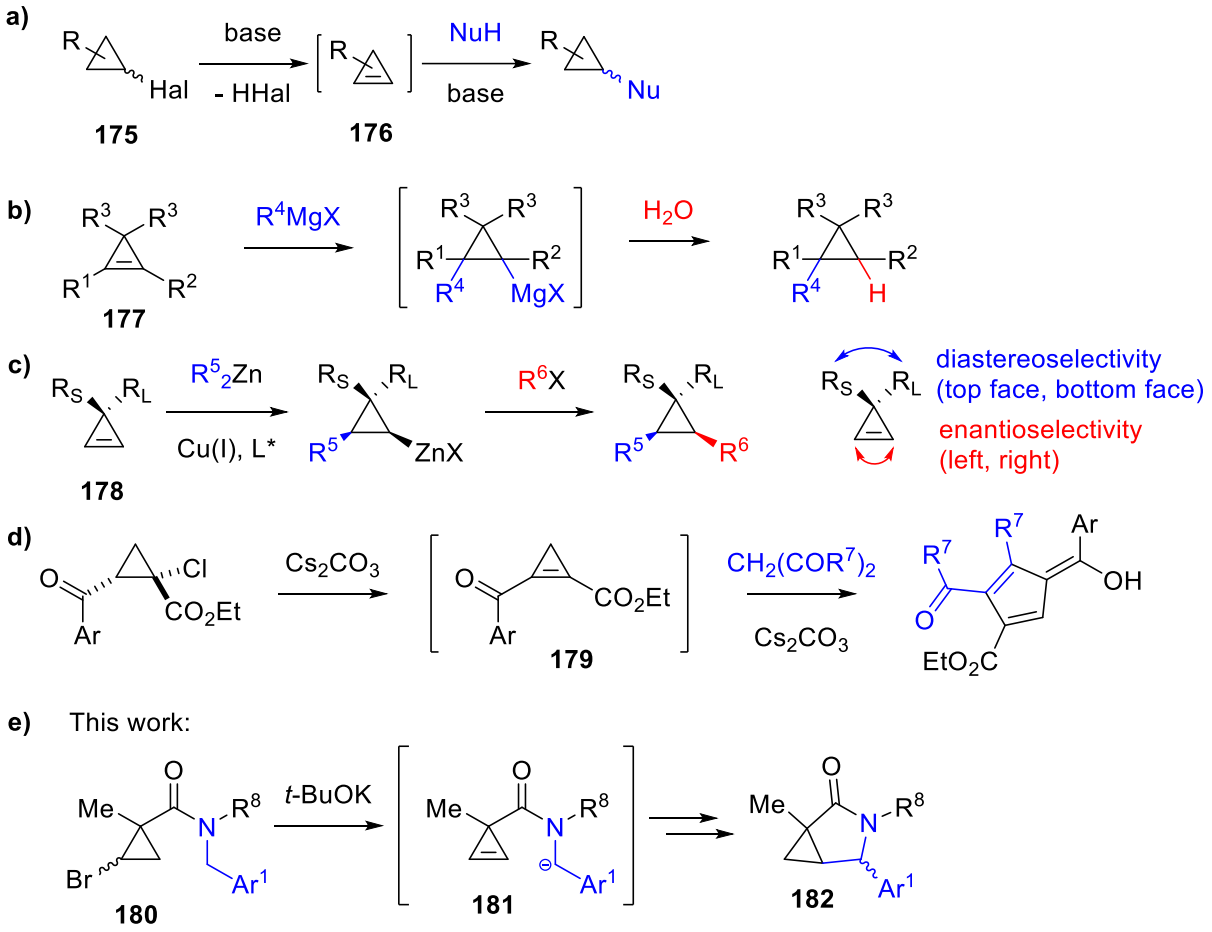
The base-assisted additions of heteroatom nucleophiles to cyclopropenes **176** generated in situ from stable halocyclopropanes **175** have emerged as a convenient route towards complex cyclopropyl scaffolds,[116] complementary to existing transition metal-catalyzed methodologies (Scheme 45a).[117,118]

Oxygen-,[111,114, 119] nitrogen-,[107,114, 120] sulfur-, [121] or halogen-based [122] entities have been successfully added, in either an inter- or an intramolecular fashion.[123] The employment of carbon-based nucleophilic species in non-catalyzed transformations of these types has thus far been less abundant. The apparent challenges associated with a strong basicity of organometallic reagents on the one hand, and a lower reactivity of stabilized carbon nucleophiles, such as enolates, toward non-conjugate cyclopropenes on the other hand, have limited the application of this chemistry.

The addition of strong carbon nucleophiles (organometallic reagents) to cyclopropenes (**177**) has been known since the 1970s (Scheme 45b). [124] An enantioselective variant of these transformation exploiting a copper-catalyzed carbozincation 3,3-disubstituted cyclopropenes **178** was later shown by Marek (Scheme 45c).[125] Recently, Gong demonstrated the Michael addition of enolates to highly activated conjugate cyclopropenyl ketone **179** generated in situ, which was accompanied by the cleavage of the three-membered ring (Scheme 45d).[126]

In this work, we explore an intramolecular addition of nitrogen ylides, generated from *N*-benzylcarboxamides **180** to non-conjugated cyclopropenes **181** (Scheme 45e).

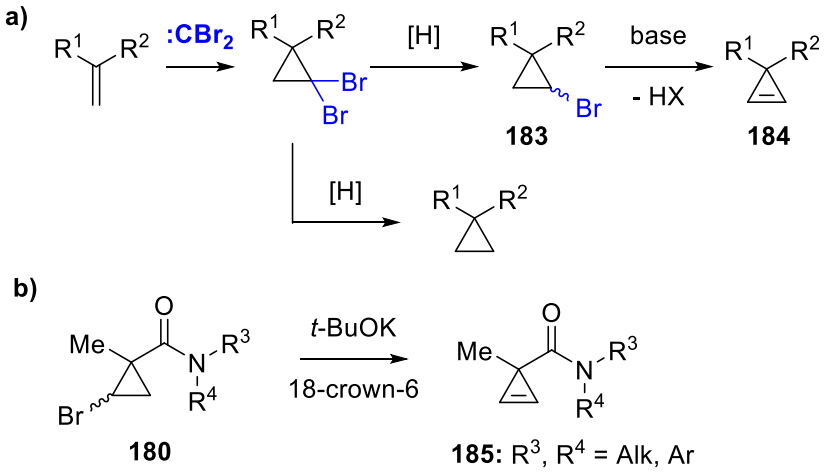
Scheme 45



3.2 Unexpected rearrangement of cyclopropene *N*-benzyl carboxamides

Previously it was demonstrated that a very efficient 1,2-dehydrohalogenation of bromocyclopropanes **183** en route to cyclopropenes **184** could be achieved using mild alkoxide bases in THF in the presence of catalytic amounts of 18-crown-6 ether (Scheme 46).[115a] Compared to the classical protocol in dry DMSO this modification allowed for more convenient isolation and improved overall yields of cyclopropenes. This proved to be particularly beneficial for the synthesis of functionalized cyclopropenes, such as tertiary carboxamides **185** bearing an alkyl group and an electron rich aryl group (Scheme 46b).[115a]

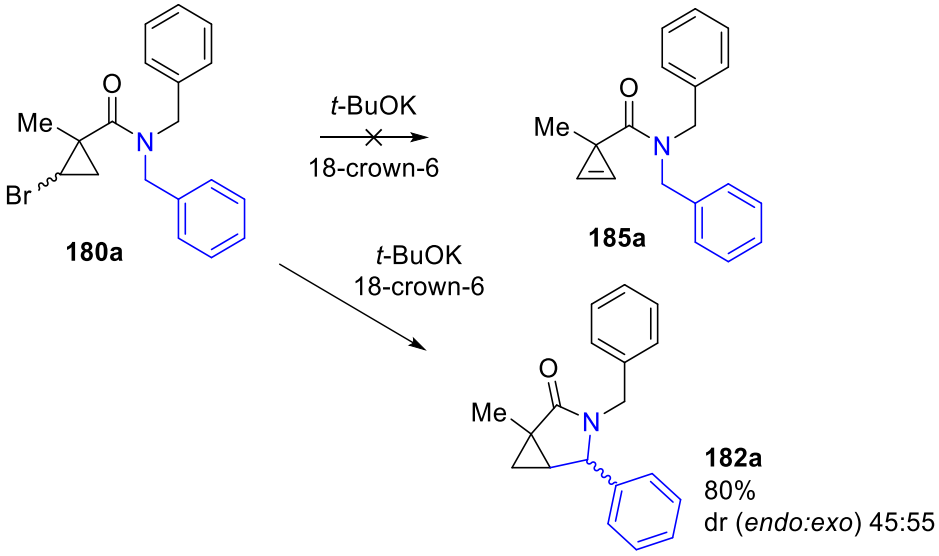
Scheme 46



In course of continuous efforts to expand the scope of available cyclopropenes **184** obtained through well-established dehydrohalogenation of bromocyclopropanes **183**, we discovered an unusual reaction, involving a formal intramolecular nucleophilic substitution of bromocyclopropanes with nitrogen ylides **181** generated in situ from *N*-benzyl carboxamides **180** (Scheme 47).

In attempt to obtain *N*,*N*-benzyl substituted cyclopropeneamide **185a** we subjected corresponding bromocyclopropane **180a** to standard reaction conditions (Scheme 47). Surprisingly, instead of olefin **185a**, a mixture of diastereomeric lactams **182a** was produced in ca. 60% yield.[127] Employing excess of freshly sublimed *tert*-butoxide and carrying out the reaction under strictly anhydrous conditions allowed for the improvement of the yield up to 80%, but did not affect the diastereomeric composition of the product (Scheme 47).

Scheme 47



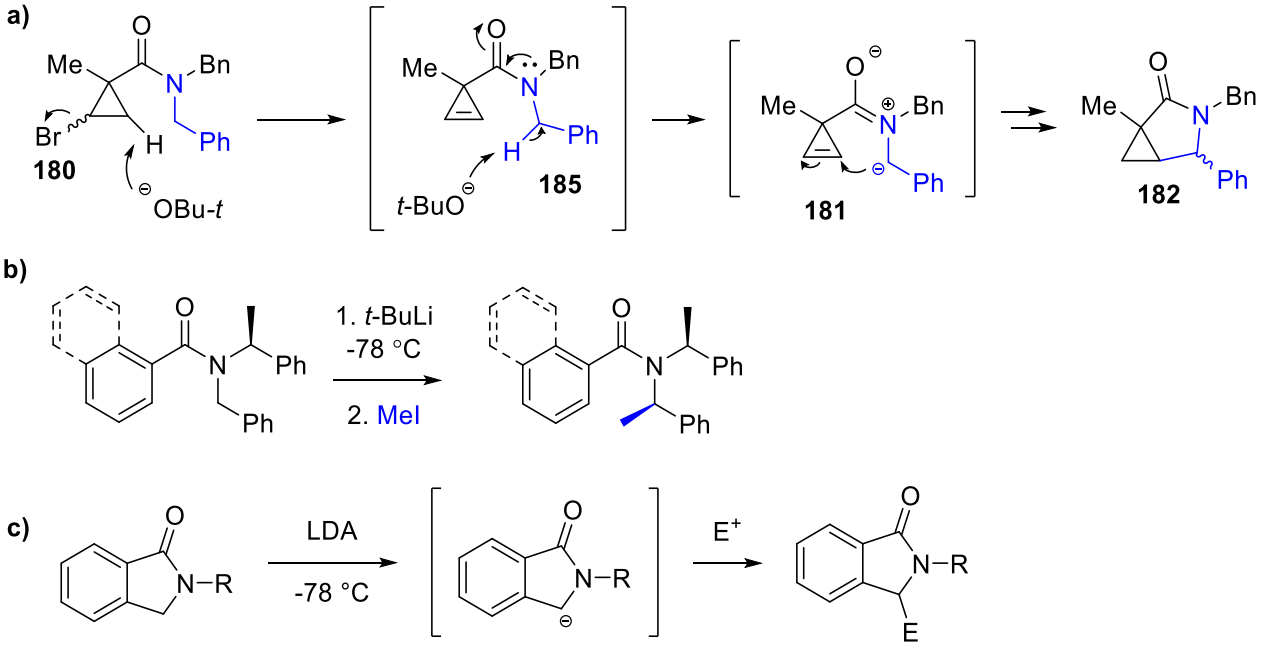
This transformation represents an intramolecular, ring-retentive 5-*exo-trig* cyclization of non-conjugated cyclopropenes **181** with nitrogen ylides, generated from *N*-benzylcarboxamides **181** in the presence of relatively mild alkoxide bases. This process allowed for the straightforward and highly expeditious assembly of biologically relevant 3-azabicyclo[3.1.0]hexan-2-one scaffolds, although in only moderate yields and selectivity. This was a pleasant surprise, since this scaffold occurs in nature[128] and has significant importance for medicinal chemistry[129] and synthetic methodology.[130]

3.3 Intramolecular nucleophilic addition of carbanions generated from *N*-benzylamides to cyclopropenes

This unexpected 5-*exo-trig* cyclization was apparently triggered by the base-assisted deprotonation at the benzylic position of cyclopropene intermediate **185a** (Scheme 48a). The formation of anionic species in an α-position to nitrogen in carboxamides is well precedented.[131]

Stoichiometric deprotonation needed for intermolecular alkylation normally requires strong organometallic bases such as *t*-BuLi or *n*-BuLi (Scheme 48b).[131] For intramolecular reactions, however, the use of LDA and even *t*-BuOK has also been reported to be particularly successful in the Hurtly arylation (Scheme 48c).[132]

Scheme 48

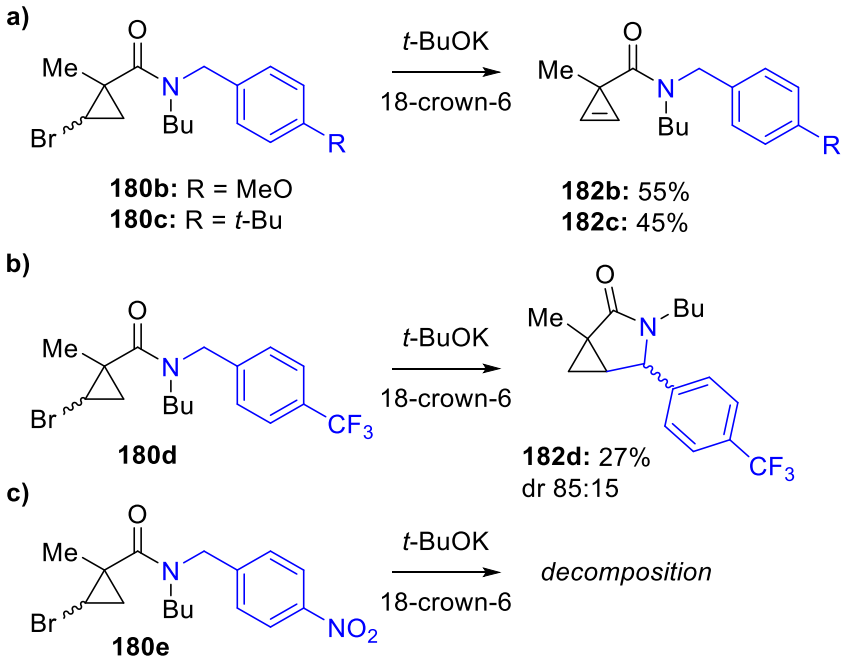


In order to provide support to this mechanism, we reasoned that lowering the C–H acidity of the benzylic group would prevent formation of benzylic anion thus shutting down the 5-*exo*-*trig* cyclization pathway and divert reaction to the initially desired dehydrohalogenation. Indeed, bromocyclopropanes **180b,c** possessing electron-donating substituents in an aromatic ring produced the corresponding cyclopropenes **185b,c** as sole isolable products in moderate yields (Scheme 49a).

On the contrary, incorporation of strong electron-withdrawing substituents would lead to the

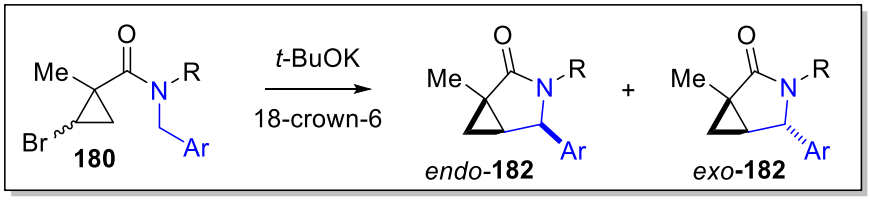
stabilization of the benzylic anion and thus result in reduced nucleophilicity, which would make the cyclization pathway inefficient. Hence, the reaction of **180d**, bearing a CF_3 group in the *para*-position, afforded a very poor yield of bicyclic product **182d** (Scheme 49b), while *para*-NO_2 analog **180e** simply decomposed under the reaction conditions (Scheme 49c).

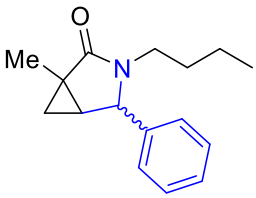
Scheme 49



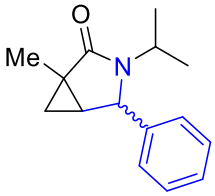
To our delight, substrates possessing neutral or moderately electron-withdrawing substituents cyclized smoothly affording the corresponding 3-azabicyclo[3.1.0]hexan-2-ones in moderate to high yields (Scheme 50). Remarkably, this reaction demonstrated high tolerance to steric hindrance at the nitrogen atom, as we were able to efficiently cyclize the substrates bearing (a) primary, Me (**180j**– **180m**) and *n*-Bu (**180f**); (b) secondary, *i*-Pr and Cy (**180h,g**, respectively); and (c) tertiary, *t*-Bu (**180i**) groups. Interestingly, steric hindrance on the nitrogen atom influences diastereoselectivity; however, this effect is quite weak.

Scheme 50

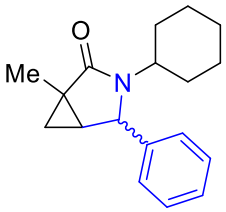




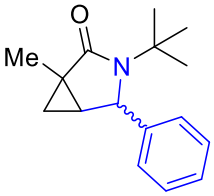
182f: 70%
dr (*endo:exo*) 53:47



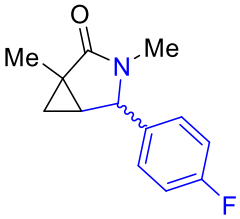
182g: 65%
dr (*endo:exo*) 50:50



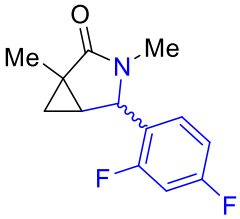
182h: 75%
dr (*endo:exo*) 45:55



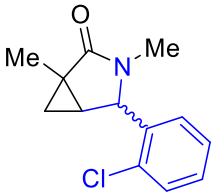
182i: 64%
dr (*endo:exo*) 47:53



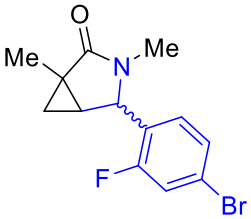
182j: 58%
dr (*endo:exo*) 60:40



182k: 75%
dr (*endo:exo*) 69:31



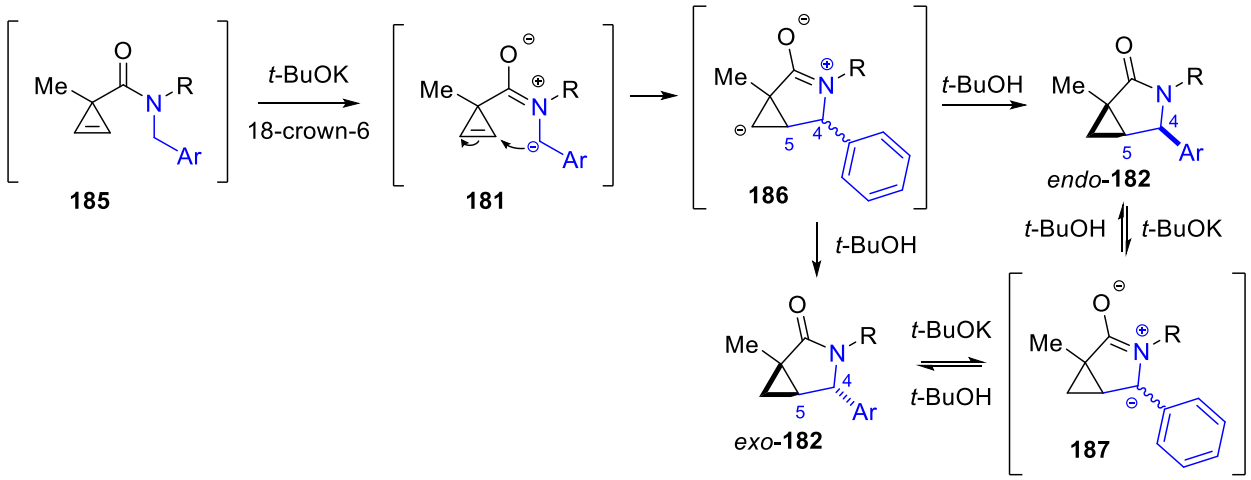
182l: 69%
dr (*endo:exo*) 70:30



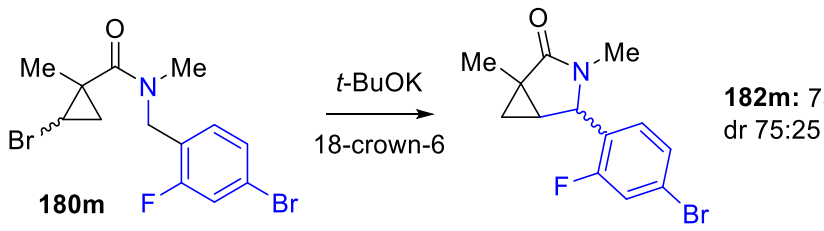
182: 75%
dr (*endo:exo*) 75:25

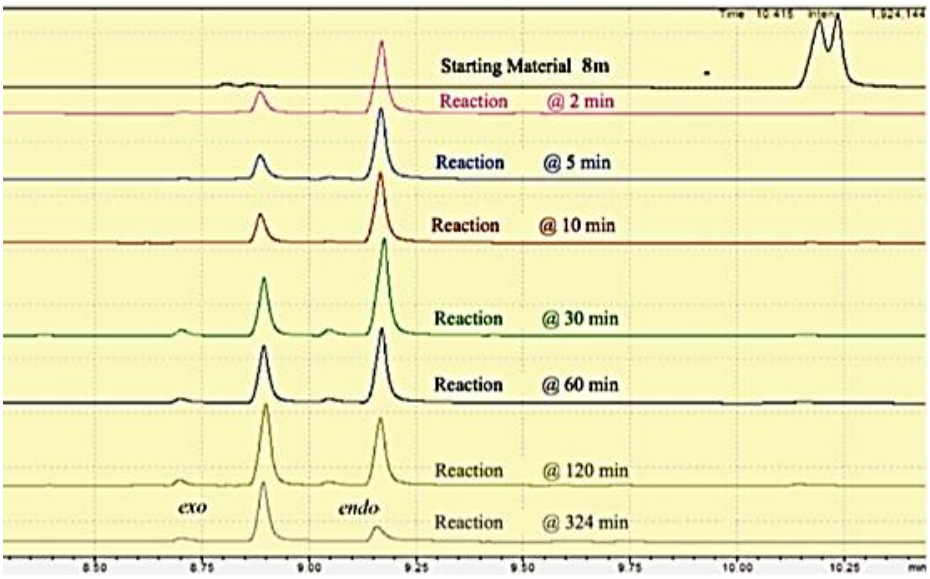
Unfortunately, all of the bicyclic products **182** were obtained as mixtures of *endo*- and *exo*-diastereomers. This was to be expected, considering the relatively high acidity of the tertiary benzylic C–H group at C-4 in final cyclic products, and the possibility of a facile base-assisted epimerization under the reaction conditions. The cyclization of ylide **181**, generated by the deprotonation of cyclopropenyl amide **185**, should provide cyclopropyl anion **186** (Scheme 51). Subsequent protonation affords a mixture of *exo*-**182** and *endo*-**182** products, and their initial ratio depends on stereo-electronic factors at the cyclization step. However, the final product ratio is determined by a thermodynamic equilibrium that occurs via stabilized cyclic ylide **187**.

Scheme 51



Scheme 52

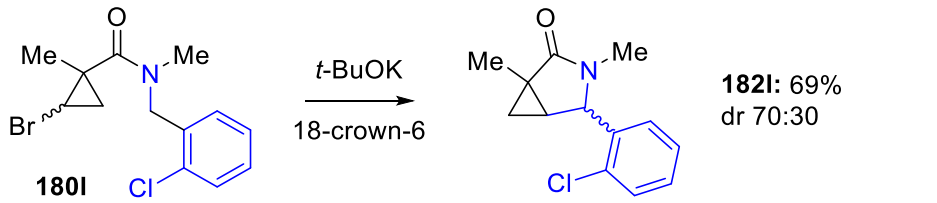


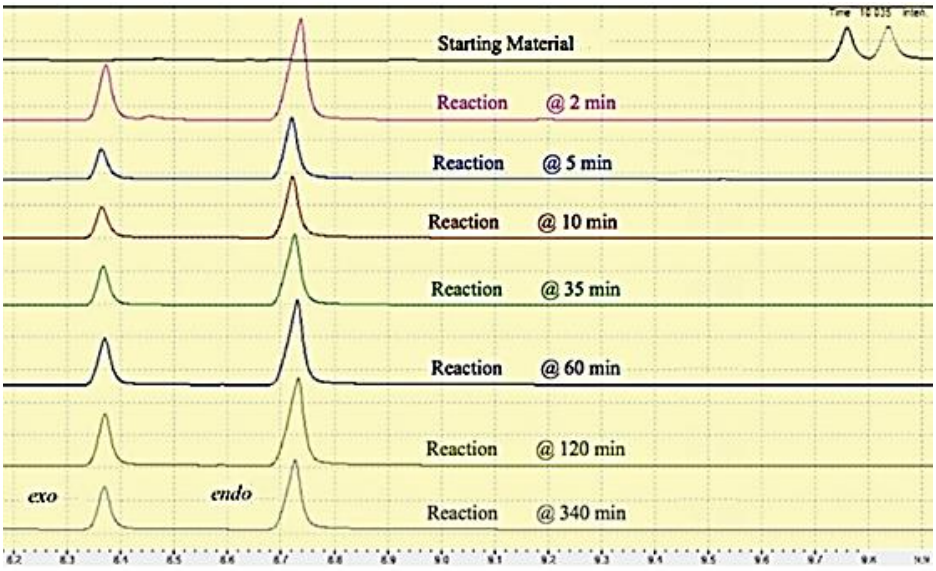


The *exo*-/*endo*-ratio change can be monitored in time by GC (shown for compound **182m**, Scheme 52). Results of the GC-monitoring for cyclization reactions were used to choose the best reaction duration and the appropriate quenching time for each particular product. In some cases,

such as with *ortho*-chlorinated derivative **182l**, deprotonation at C-4 cannot be achieved efficiently due to steric hindrance, so the final diastereomeric ratio matches that for the initialy observed distribution (Scheme 53).

Scheme 53





The low degrees of diastereoselectivity can be attributed to the too small difference in the thermodynamic stabilities of *endo*- and *exo*-diastereomers of the cyclized product in five-membered scaffold **182**. Our DFT modeling showed that *exo*-**182j** is more stable than *endo*-**182j** by only 1.50 kcal mol^{-1}, which corresponds to the best typically achieved dr of around 70 : 30.[2] Also, this modeling helped to assign relative configurations of the diastereomeric bicyclic products. Indeed, calculation showed that dihedral angles between (C-4)–H and (C-5)–H bonds in *endo*- and *exo*-isomers are 36.8 ° and 94.4 °, respectively.[2] This suggests that the value of the

corresponding vicinal spin–spin coupling constants for *endo*-isomers should be larger. Indeed, the benzylic proton signals in the ^{1}H NMR spectra appeared as doublets for the isomers (*endo*) and as singlets for another one (*exo*).

Also, the relative configuration of *exo*-**182j** was independently and unambiguously assigned by single-crystal X-ray diffraction (Figure 13).

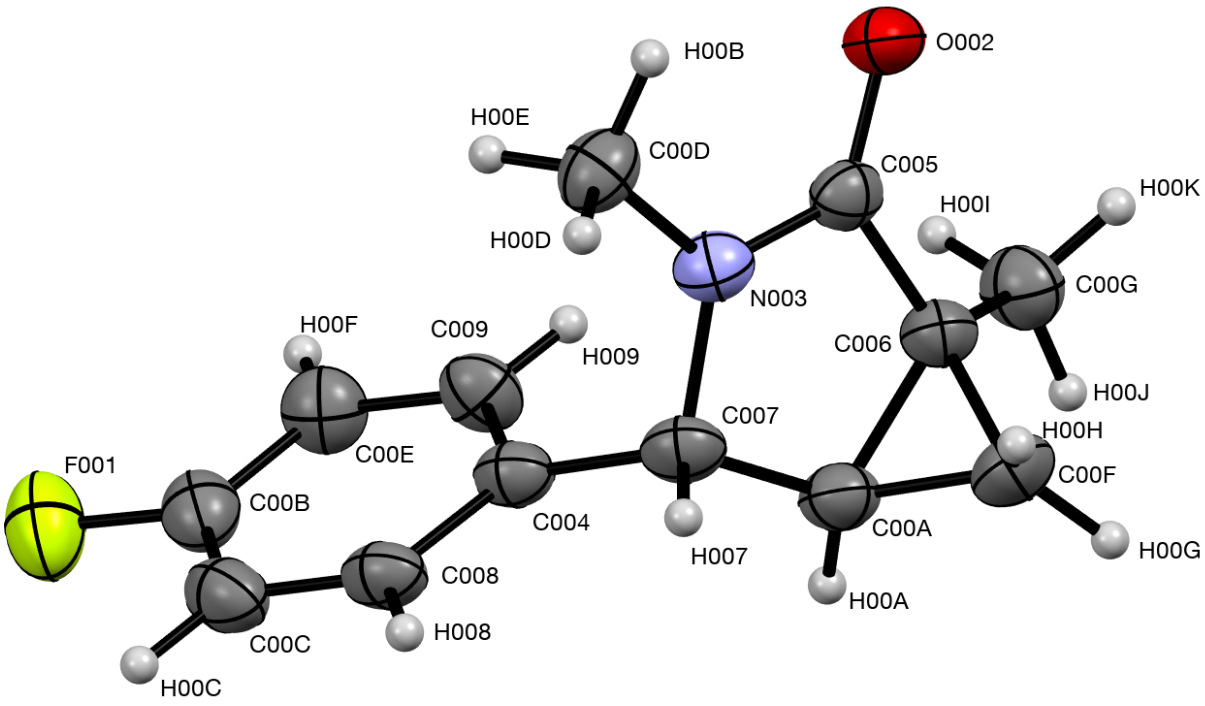


Figure 13. X-ray crystal structure of compound *exo*-**182j** (CCDC #1575277)

3.4 Conclusion

A cascade, base-assisted dehydrohalogenation/5-*exo*-*trig* nucleophilic cyclization of stabilized benzylic anions to cyclopropenes was discovered. This reaction represents the first example of the non-catalytic addition of carbon nucleophiles to unactivated cyclopropenes. The obtained results are valuable as a proof of concept and are being applied in design of the diastereoselective

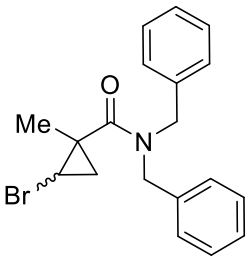
cyclization of carbon-based nucleophiles to obtain six- and seven-membered ring systems. The latter models are expected to allow for better stereo-electronic control, due to a more substantial difference in the thermodynamic stabilities of the corresponding diastereomers.

3.5 Experimental

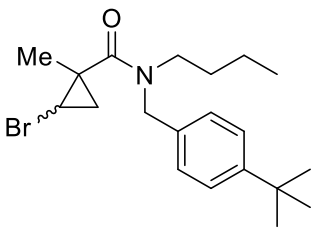
3.5.1 General information

NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (500 MHz) equipped with a dual carbon/proton cryoprobe (CPDUL) or with a BBO probe or on a Bruker Avance DPX-400 spectrometer (400 MHz) equipped with a quadrupleband gradient probe (H/C/P/F QNP). ^{13}C NMR spectra were recorded with broadband decoupling. IR spectra were recorded on a ThermoFisher Nicolet™ iS™ 5 FT-IR spectrometer. HRMS was carried out on a LCT Premier (Micromass Technologies) instrument employing ESI TOF detection techniques. Glassware used in moisture-free syntheses was flame dried under vacuum prior to use. Column chromatography was carried out on silica gel (Sorbent Technologies, 40–63 mm). Pre-coated silica gel plates (Sorbent Technologies Silica XG 200 mm) were used for TLC analyses. Anhydrous THF and dichloromethane (DCM) were obtained by the distillation of a degassed commercially available HPLC-grade inhibitor-free solvent over calcium hydride and stored over 4 Å molecular sieves under nitrogen. Commercial potassium *tert*-butoxide was sublimed under vacuum prior to use. The syntheses of new bromocyclopropanes starting materials **180a–m** are described in chapter 3.5.2. 2-Bromo-1-methylcyclopropane-1-carbonyl chloride was synthesized according to the procedure previously published by our group[115] and had physical and spectral properties identical to those earlier reported. All other reagents and solvents were purchased from commercial vendors and used as received.

3.5.2 Syntheses of bromocyclopropanes

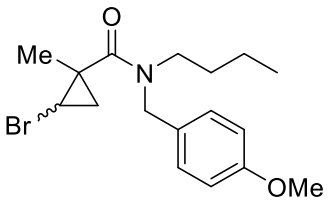


N,N-Dibenzyl-2-bromo-1-methylcyclopropane-1-carboxamide (**180a**), Typical procedure: 2-Bromo-1-methylcyclopropane-1-carbonyl chloride (494 mg, 2.50 mmol) in anhydrous DCM (7 mL) was added dropwise to a solution of dibenzylamine (493 mg, 2.50 mmol) and triethylamine (706 µL, 512 mg, 5.07 mmol) in anhydrous DCM (4 mL) stirred in a flame dried Schlenk flask under a nitrogen atmosphere. The reaction was stirred overnight at rt. The solvent was then evaporated in vacuum, and the residue was triturated with THF (7 mL). The precipitate was removed by suction filtration and the filter cake was rinsed with THF (2 x 4 mL). Then the precipitate was dissolved in H_2O (20 mL) and extracted with EtOAc (2 x 4 mL). The combined organic phases were washed with brine (20 mL, dried with $MgSO_4$, combined with the THF filtrate, and concentrated. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (6:1) as a yellow oil (R_f 0.29). Yield 553.4 mg (1.54 mmol, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.51–7.48 (m), 7.42–7.27 (m), 7.25–7.06 (m), ∑10H], [5.25 (d, *J* = 14.5 Hz), 4.98 (d, *J* = 16.6 Hz), 4.73–7.46 (m), 4.37 (d, *J* = 16.7 Hz), 3.91 (d, *J* = 14.5 Hz), ∑4H], [3.24 (dd, *J* = 8.2, 4.9 Hz), 3.00 (dd, *J* = 7.5, 4.7 Hz), ∑1H], [1.81 (dd, *J* = 8.2, 6.7 Hz), 1.76–1.73 (m), ∑1H], [1.53 (s), 1.40 (s), ∑3H], [1.25 (t, *J* = 7.1 Hz), 0.95 (dd, *J* = 6.7, 4.9 Hz), ∑1H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ (172.5, 171.3, 1C), (136.7, 136.1, 2C), (129.1, 128.9, 4C), (128.3, 127.1, 4C), (127.6, 127.4, 2C), (49.8, 47.5, 1C), [49.6 (br.), 47.1 (br.), 1C], 28.0 (1C), (27.3, 26.1, 1C), (22.7, 21.9, 1C), (22.1, 19.8, 1C); FT IR (NaCl, cm^{-1}): 3062, 3030, 2929, 1643, 1495, 1453, 1421, 1325, 1299, 1205, 1185, 1079, 1029, 1013, 749, 698; HRMS (TOF ES): found 358.0810, calculated for $C_{19}H_{21}BrNO$ (M + H) 358.0807 (0.8 ppm); EA found C 63.83, 63.58, H 5.43, 5.93, N 4.14, 3.90, calculated for $C_{19}H_{20}BrNO$: C 63.70, H 5.63; N 3.91.



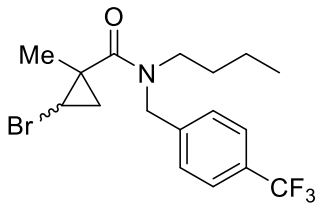
2-Bromo-N-butyl-N-(4-(tert-butyl)benzyl)-1-methylcyclopropane-1-carbox- amide (**180b**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (545 mg, 2.76 mmol), *N*-(4-(*tert*-butyl)benzyl)butan-1-amine (605 mg, 2.76 mmol), and triethylamine (1.40 mL, 1.02 g, 10.5 mmol). The reaction mixture was stirred at room temperature overnight. After standard aqueous workup and extraction, the material was filtered through a silica plug to give a pale-yellow glass, yield 882 mg (2.32 mmol, 84%). This material had purity by GC c.a. 98% and could be used in the cyclization step as is without additional purification. If desired, diastereomeric bromocyclopropanes can be additionally purified and separated by preparative column chromatography on Silica gel eluting with a CH_2Cl_2/EtOAc mixture (40:1). Individual isomers were isolated as colorless crystals (*trans*-**180b**) and colorless glass (*cis*-**180b**), respectively. NMR spectra of both diastereomers showed signals of two rotamers. Analysis of signals in proton spectra of *cis*-**180b** is complicated by severe broadening of the lines, which can be partially resolved by measuring ^{1}H NMR spectrum in benzene-d_6 at 75 °C. ***trans*-180b**: mp 93.3-93.8 °C; R_f 0.37 (CH_2Cl_2/EtOAc 40:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.38 (d, *J* = 8.2 Hz), 7.30 (d, *J* = 8.2 Hz), ∑2H], [7.21 (d, *J* = 8.2 Hz), 7.17 (d, *J* = 8.1 Hz), 7.09 (d, *J* = 8.2 Hz), ∑2H], [5.04 (d, *J* = 16.8 Hz), 4.81 (d, *J* = 15.0 Hz), 4.63 (br.m), 4.46 (d, *J* = 16.3 Hz) , ∑2H], [3.80 (ddd, *J* = 14.2, 10.8, 5.6 Hz), 3.53 (ddd, *J* = 13.9 11.5, 4.9 Hz), 3.25 (ddd, *J* = 14.1, 11.4, 4.9 Hz), 3.04–2.95 (m), 2.75 (ddd, *J* = 13.3, 10.0, 5.4 Hz) , ∑3H], [1.80–1.70 (m), 1.71–1.64 (m), 1.63–1.52 (m), 1.52–1.43 (m), 1.26–1.16 (m), ∑6H], [1.42 (s), 1.32 (s), ∑3H], [1.32 (s), 1.29 (s), ∑9H], [0.92 (t, *J* = 7.4 Hz), 0.86 (t, *J* = 7.3 Hz), ∑3H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ (170.7, 170.6, 1C), (150.5, 150.1, 1C), (134.2, 133.8, 1C), (127.8,

126.5, 2C), (125.8, 125.3, 2C), (50.5, 47.3, 1C), (46.7, 45.4, 1C), (34.6, 34.6, 1C), 31.5 (3C), (30.5, 28.7, 1C), (28.2, 28.1, 1C), (26.3, 26.2, 1C), (22.7, 22.6, 1C), 22.1, 20.4, (14.0, 14.0 1C). ***cis*-180b**: R_f 0.27 (CH_2Cl_2/EtOAc 40:1); ^{1}H NMR (500 MHz, C_6D_6 at 75 °C) δ 7.26 (d, *J* = 8.3 Hz, 2H), 7.07 (br. s, 2H), 4.51 (br. s, 1H), 4.44 (d, *J* = 15.2 Hz, 1H), 3.29–3.04 (br. m, 3H), 1.70 (dd, *J* = 8.1, 6.5 Hz, 1H), [1.36 (s), 1.22 (s), ∑9H], 1.40–1.28 (m, 4H), 1.23 (br. s, 1H), 1.13–1.01 (m, 2H), 0.76 (t, *J* = 7.4 Hz, 3H), 0.65 (dd, *J* = 6.6, 4.9 Hz, 1H). ^{1}H NMR (500 MHz, $CDCl_3$ at RT) δ 7.38–7.30 (br. m, 2H), [7.28–7.25 (br.m), 7.13–7.05 (br. m), ∑2H], [4.65 (br.d, *J* = 16.3 Hz), 4.43 (br. d, *J* = 15.2 Hz), ∑2H], 3.35–3.14 (br.m, 3H), [1.76 (br.m), 1.68 (br.m), 1.57 (br.m), 1.50 (br.s), ∑6H], 1.32 (br.s, 11H), 1.00–0.78 (br.m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$ at RT) δ 172.1, (150.7, 150.3, 1C), (134.2, 133. 5, 1C), (127.5, 126.5, 2C), (125.9, 125.7, 2C), (50.3, 46.7, 1C), (46.3, 44.6, 1C), 34.6, 31.5 (3C), (30.2, 29.0, 1C), (27.8, 27.7, 1C), (26.3, 26.2, 1C), 21.9, (20.3, 20.2, 1C), (20.0, 19.9, 1C), 14.0. HRMS (TOF ES): found 402.1416, calculated for $C_{20}H_{30}BrNONa$ (M + Na) 402.1408 (2.0 ppm). EA found C 63.05, 63.27, H 7.78, 8.03, N 3.87, 3.59, calculated for $C_{20}H_{30}BrNO$: C 63.15, H 7.95; N 3.68.



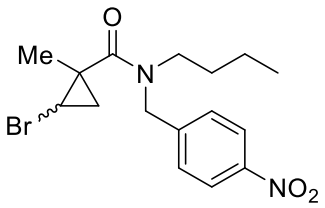
2-Bromo-N-butyl-N-(4-methoxybenzyl)-1-methylcyclopropane-1-carboxamide (**180c**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (584 mg, 2.96 mmol), *N*-(4-methoxybenzyl)butan-1-amine (572 mg, 2.96 mmol), and triethylamine (1.40 mL, 1.02 g, 10.5 mmol). The reaction mixture was stirred at room temperature overnight. After standard aqueous workup and extraction, the material was filtered through a silica plug to give a pale orange oil, yield 912 mg (2.58 mmol, 87%). This material had purity by GC c.a. 98% and could be used in the cyclization step as is without additional purification.

If desired, it can be additionally purified by preparative column chromatography on Silica gel eluting with a CH_2Cl_2/EtOAc mixture (20:1) to isolated inseparable mixture of diastereomeric bromo- cyclopropanes **180c** as colorless oil, R_f 0.45 (CH_2Cl_2/EtOAc 20:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.22 (d, *J* = 8.6 Hz), 7.17 (d, *J* = 8.5 Hz), 7.09 (br.m), ∑2H], [6.91 (d, *J* = 8.6 Hz), 6.95–6.79 (br.m), 6.82 (d, *J* = 8.6 Hz), ∑2H], [5.00 (d, *J* = 16.5 Hz), 4.86 (d, *J* = 14.7 Hz), 4.61 (br.m), 4.44 (d, *J* = 16.6 Hz), 4.40 (br.m), 4.34 (d, *J* = 14.8 Hz), ∑2H], [3.81 (s), 8.80 (br.s), 3.78 (s), ∑3H], [3.78–3.69 (m), 3.51 (ddd, *J* = 14.1, 11.6, 4.9 Hz), 3.27 (br.m), 3.22–3.15 (m), 3.00 (ddd, *J* = 7.3, 4.7, 2.5 Hz), 2.76 (ddd, *J* = 13.4, 10.0, 5.4 Hz), ∑2H], [1.80–1.70 (m), 1.70–1.64 (m), 1.62–1.49 (m), 1.46–1.41 (m), 1.33–1.15 (m), ∑7H], [1.48 (s), 1.40 (s), 1.33 (s), ∑3H], [0.93 (t, *J* = 7.4 Hz), 0.86 (t, *J* = 7.4 Hz), ∑3H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ (172.0, 170.7, 1C), (159.1, 158.9, 1C), (129.7, 129.3, 128.1, 2C), (129.5, 128.7, 128.0, 1C), (114.4, 114.3, 114.1, 113.8, 2C), (55.4, 55.4, 55.3, 1C), (50.3, 50.1, 46.9, 46.5, 1C), (46.4, 46.1, 45.2, 44.5, 1C), (30.4, 30.2, 29.0, 28.7, 1C), (28.2, 28.2, 1C), (27.8, 27.6, 26.3, 26.2, 1C), (22.7, 22.6, 21.8, 1C), (22.0, 20.0, 19.8, 1C), (20.4, 20.3, 1C), (14.0, 14.0, 14.0, 1C); HRMS (TOF ES): found 376.0900, calculated for $C_{17}H_{24}BrNO_2Na$ (M + Na) 376.0888 (3.2 ppm). EA found C 57.83, 57.57, H 6.58, 6.96, N 3.94, 4.01, calculated for $C_{17}H_{24}BrNO_2$: C 57.63, H 6.83; N 3.95.



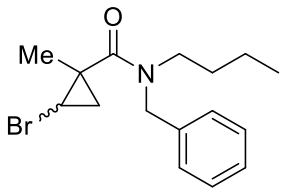
2-Bromo-N-butyl-1-methyl-N-(4-(trifluoromethyl)benzyl)cyclopropane-1-carboxamide (**180d**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (1.00 g, 5.06 mmol), *N*-(4-(trifluoromethyl)benzyl)butan-1-amine (1.17 g, 5.06 mmol), and triethylamine (1.39 mL, 1.01 g, 10.0 mmol). The reaction mixture was stirred at room temperature overnight. The product was

isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:1) as a colorless oil (R_f 0.34). Yield: 1.73 g (4.40 mmol, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.64 (d, *J* = 7.9 Hz), 7.54 (d, *J* = 7.9 Hz), ∑2H], 7.39 (m, 2H), [5.11 (d, *J* = 17.3 Hz), 4.90 (d, *J* = 15.3 Hz), 4.56 (d, *J* = 17.4 Hz), 4.47 (d, *J* = 15.3 Hz), ∑2H], [3.83 (ddd, *J* = 13.7, 10.2, 5.6 Hz), 3.60 (ddd, *J* = 14.3, 11.7, 4.9 Hz), 3.22 (ddd, *J* = 14.3, 11.5, 4.8 Hz), 3.02 (ddd, *J* = 15.6, 7.5, 4.7 Hz), 2.70 (ddd, *J* = 13.6, 10.1, 5.2 Hz), ∑3H], [1.76–1.70 (m), 1.67 (t, *J* = 5.8 Hz), 1.63–1.44 (m), 1.42 (s), 1.36–1.28 (m), 1.26 (s), 1.25–1.17 (m), ∑9H], [0.93 (t, *J* = 7.3 Hz), 0.86 (t, *J* = 7.3 Hz), ∑3H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ (171.0, 170.8, 1C), (141.7, 141.3, 1C), [129.6 (q, $^2J_{CF}$ = 32.6 Hz), 129.4 (q, $^2J_{CF}$ = 32.4 Hz), 1C], (128.3, 127.1, 2C), [126.0 (q, $^3J_{CF}$ = 3.8 Hz), 125.4 (q, $^3J_{CF}$ = 3.8 Hz), 2C], [125.3 (q, $^1J_{CF}$ = 272.5 Hz), 124.2 (q, $^1J_{CF}$ = 271.4 Hz), 1C], (50.5, 47.7, 1C), (47.3, 45.7, 1C), (30.6, 28.6, 1C), (28.11, 28.05, 1C), (26.2, 26.0, 1C), (22.7, 22.6, 1C), (21.9, 21.8, 1C), 20.4 (1C), (13.98, 13.95, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.45, -62.51; FT IR (NaCl, cm^{-1}): 2962, 2935, 2874, 1644, 1416, 1326, 1164, 1125, 1067, 1018, 824; HRMS (TOF ES): found 414.0636, calculated for $C_{17}H_{21}BrF_3NONa$ (M + Na) 414.0656 (4.8 ppm); EA found C 52.25, 51.88, H 5.64, 5.28, N 3.28, 3.70, calculated for $C_{17}H_{21}BrF_3NO$: C 52.05, H 5.40, N 3.57.



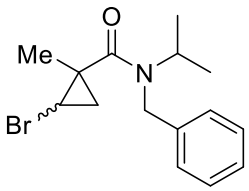
2-Bromo-N,1-dimethyl-N-(4-nitrobenzyl)cyclopropane-1-carboxamide (**180e**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (494 mg, 2.50 mmol), *N*-methyl-1-(4- nitrophenyl)methanamine (415 mg, 2.50 mmol), and triethylamine (886 μL 642 mg, 6.35 mmol). The reaction mixture was stirred at room temperature overnight. The product was isolated by column chromatography eluting with a

hexanes/EtOAc mixture (1:3) as a yellow oil (R_f 0.38). Yield: 458 mg (1.40 mmol, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30–8.14 (m, 2H), [7.52 -7.44 (m), 7.37 (d, *J* = 8.7 Hz), ∑2H], [5.24 (d, *J* = 17.4 Hz), 4.93 (d, *J* = 14.7 Hz), 4.70–4.54 (m), 4.50 (d, *J* = 14.7 Hz), ∑2H], [3.24–3.18 (m), 3.14 (s), 3.09–3.02 (m), 2.92 (s), ∑4H], [1.78 (dd, *J* = 8.2, 6.8 Hz), 1.67 (dd, *J* = 6.8, 4.7 Hz), ∑1H], [1.52 (s), 1.45 (s), 1.32 (s), ∑3H], [1.25 (t, *J* = 7.2 Hz), 0.97 (t, *J* = 5.9 Hz), ∑1H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ (172.2, 170.9, 1C), (147.4, 144.8, 1C), (128.9, 128.5, 2C), (127.4, 124.2, 1C), (124.1, 123.8, 2C), (51.1, 50.8, 1C), (35.5, 35.3, 1C), (27.7, 27.2, 1C), (26.0, 25.7, 1C), (22.4, 18.9, 1C), (21.8, 20.9, 1C); FT IR (NaCl, cm^{-1}): 2932, 2360, 1643, 1519, 1488, 1402, 1346, 1108, 935, 859, 737, 692. HRMS (TOF ES): found 349.0174, calculated for $C_{13}H_{15}BrN_2O_3Na$ (M + Na) 349.0164 (1.0 ppm); EA found C 47.43, 47.81, H 4.58, 4.90, N 8.57, 8.72, calculated for $C_{13}H_{15}BrN_2O_3$: C 47.72, H 4.62, N 8.56.



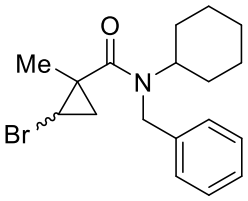
N-Benzyl-2-bromo-N-butyl-1-methylcyclopropane-1-carboxamide (**180f**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (634 mg, 3.21 mmol), *N*-benzylbutyl-1-amine (524 mg, 3.21 mmol), and triethylamine (1.40 mL, 1.02 g, 10.5 mmol). The reaction mixture was stirred at room temperature overnight. After standard aqueous workup and extraction, the material was filtered through a silica plug to give a colorless oil, yield 895 mg (2.76 mmol, 86%). This material had purity by GC c.a. 95% and could be used in the cyclization step as is without additional purification. If desired, it can be additionally purified by preparative column chromatography on Silica gel eluting with a CH_2Cl_2/EtOAc mixture (40:1) to isolated inseparable mixture of diastereomeric bromocyclopropanes **180f** as colorless oil, R_f 0.45 (CH_2Cl_2/EtOAc 40:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.22 (m, 4H), 7.16 (d, *J* = 7.2 Hz,

1H), [5.08 (d, *J* = 16.9 Hz), 4.88 (d, *J* = 14.9 Hz), 4.68 (br. m), 4.53–4.42 (m), ∑2H], [3.81 (dddd, *J* = 13.3, 10.1, 5.5, 1.5 Hz), 3.54 (ddd, *J* = 14.2, 11.8, 4.9 Hz), 3.36–3.14 (m), 3.04–2.97 (m), 2.75 (ddd, *J* = 13.4, 10.1, 5.4 Hz), ∑3H], [1.80–1.71 (m), 1.70–1.65 (m), 1.63–1.52 (m), 1.52–1.43 (br.m), 1.36–1.16 (m), ∑6H], [1.42 (s), 1.30 (s), ∑3H], [0.92 (t, *J* = 7.3 Hz), 0.86 (t, *J* = 7.4 Hz), ∑3H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ (172.2, 170.7, 1C), (137.5, 137.4, 137.0, 136.7, 1C), (129.0, 128.9, 128.8, 128.5, 2C), (128.3, 127.9, 127.7, 127.6, 1C), (127.5, 127.3, 126.8, 126.7, 2C), (50.8, 50.6, 47.7, 47.2, 1C), (46.7, 46.4, 45.5, 44.8, 1C), (30.5, 30.2, 29.0, 28.7, 1C), (28.2, 28.1, 1C), (27.7, 27.5, 26.3, 26.2, 26.1, 1C), (22.7, 22.6, 21.8, 1C), (22.0, 22.0, 20.0, 19.8, 1C), (20.4, 20.3, 1C), (14.0, 14.0, 1C); HRMS (TOF ES): found 346.0797, calculated for $C_{16}H_{22}BrNONa$ (M + Na) 346.0782 (4.3 ppm). EA found C 59.34, 59.19, H 6.68, 6.91, N 4.14, 4.43, calculated for $C_{16}H_{22}BrNO$: C 59.27, H 6.84; N 4.32.



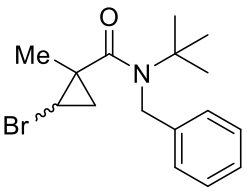
N-Benzyl-2-bromo-N-isopropyl-1-methylcyclopropane-1-carboxamide (**180g**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (667 mg, 3.38 mmol), *N*-benzylpropan-2-amine (504 mg, 3.38 mmol), and triethylamine (1.40 mL, 1.02 g, 10.5 mmol). The reaction mixture was stirred at room temperature overnight. After standard aqueous workup and extraction, the material was filtered through a silica plug to give a yellow oil, yield 860 mg (2.77 mmol, 82%). This material had purity by GC c.a. 98% and could be used in the cyclization step as is without additional purification. If desired, it can be additionally purified by preparative column chromatography on Silica gel eluting with a CH_2Cl_2/EtOAc mixture (20:1) to isolated inseparable mixture of diastereomeric bromocyclopropanes **180g** as colorless oils, R_f 0.42 (CH_2Cl_2/EtOAc 20:1). It should be pointed out, that one of the diastereomers shows in NMR

spectra two sets of signals due to restricted rotation. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.10 (m, 5H), [5.09 (d, *J* = 17.4 Hz), 4.63–4.32 (m), 3.93 (sept, *J* = 6.7 Hz), ∑3H], [3.25 (br.dd, *J* = 8.3, 5.0 Hz), 3.07 (dd, *J* = 7.6, 4.8 Hz), 2.98 (dd, *J* = 7.5, 4.7 Hz), ∑1H], [1.77 (t, *J* = 7.5 Hz), 1.71 (dd, *J* = 6.5, 5.0 Hz), ∑1H], [1.68 (s), 1.54 (br.s), 1.45 (s), 1.40 (s), ∑3H], [1.38–1.24 (m), 1.25–1.11 (m), 1.25–1.11 (m), 0.96–0.90 (m), ∑7H]. ^{13}C NMR (126 MHz, $CDCl_3$) δ (172.1, 171.3, 170.5, 1C), (139.6, 139.3, 138.5, 1C), (128.7, 128.5, 128.3, 2C), (127.4, 126.8, 1C), (127.1, 126.8, 126.6, 2C), (50.4, 49.0, 48.9, 1C), (50.3, 44.7, 44.0, 1C), (29.0, 28.6, 1C), (27.4, 26.4, 26.1, 1C), (23.3, 22.8, 21.8, 1C), (22.9, 22.3, 1C), (22.2, 22.1, 21.4, 1C), (20.2, 19.9, 19.7, 1C); HRMS (TOF ES): found 332.0638, calculated for $C_{15}H_{20}BrNONa$ (M + Na) 332.0626 (3.6 ppm). EA found C 58.30, 58.03, H 6.63, 6.54, N 4.28, 4.60, calculated for $C_{15}H_{20}BrNO$: C 58.07, H 6.50; N 4.51.



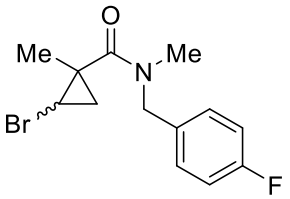
N-Benzyl-2-bromo-N-cyclohexyl-1-methylcyclopropane-1-carboxamide (**180h**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (592 mg, 3.00 mmol), *N*-benzylcyclohexylamine (568 mg, 3.0 mmol), and triethylamine (1.40 mL, 1.02 g, 10.5 mmol). The reaction mixture was stirred at room temperature overnight. After standard aqueous workup and extraction, the material was filtered through a silica plug to give a pale-yellow oil, yield 893 mg (2.55 mmol, 85%). This material had purity by GC c.a. 96% and could be used in the cyclization step as is without additional purification. If desired, it can be additionally purified by preparative column chromatography on Silica gel eluting with a CH_2Cl_2/EtOAc mixture (40:1) to isolated inseparable mixture of diastereomeric bromocyclopropanes **180h** as colorless oils, R_f 0.40 (CH_2Cl_2/EtOAc 40:1). It should be pointed out, that one of the diastereomers shows in NMR

spectra two sets of signals due to restricted rotation. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.12 (m, 5H), [5.09 (d, *J* = 17.6 Hz), 4.61 (s), 4.57 (s), 4.44 (d, *J* = 17.6 Hz), 4.36 (d, *J* = 15.6 Hz), ∑2H], [3.95 (tt, *J* = 11.4, 3.1 Hz), 3.88–3.76 (m), ∑1H], [3.23 (dd, *J* = 8.1, 4.9 Hz), 3.08 (dd, *J* = 7.6, 4.8 Hz), 2.96 (dd, *J* = 7.5, 4.6 Hz), ∑1H], [2.02 (br.d, *J* = 11.8 Hz), 1.89–1.75 (m), 1.74–1.62 (m), 1.62–1.29 (m), 1.26–1.20 (m), 1.17–0.90 (m), ∑12H], [1.43 (s), 1.27 (s) ∑3H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ (172.2, 171.3, 170.6, 1C), (139.6, 139.3, 138.9, 1C), (128.6, 128.4, 128.3, 2C), (127.3, 126.8, 1C), (127.2, 126.7, 126.6, 2C), (58.2, 58.2, 57.8, 1C), (49.7, 45.8, 45.1, 1C), (33.5, 32.5, 30.4, 1C), (32.8, 32.2, 30.0, 1C), (28.9, 28.7, 1C), (27.6, 26.3, 26.2, 1C), (26.3, 26.2, 26.2, 26.1, 26.1, 2C), (25.7, 25.5, 25.5, 1C), (23.5, 23.1, 21.6, 1C), (22.3, 22.2, 20.0, 1C); HRMS (TOF ES): found 372.0947, calculated for $C_{18}H_{24}BrNONa$ (M + Na) 372.0939 (2.1 ppm). EA found C 61.53, 61.91, H 7.03, 7.11, N 4.09, 4.15, calculated for $C_{18}H_{24}BrNO$: C 61.72, H 6.91; N 4.00.



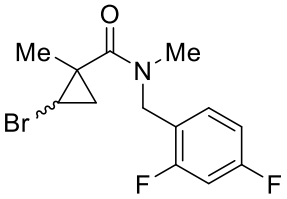
N-Benzyl-2-bromo-N-(tert-butyl)-1-methylcyclopropane-1-carboxamide (**180i**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (640 mg, 3.24 mmol), *N*-benzyl-2-methylpropan-2-amine (529 mg, 3.24 mmol), and triethylamine (1.40 mL, 1.02 g, 10.5 mmol). The reaction mixture was stirred at room temperature overnight. After standard aqueous workup and extraction, the material was filtered through a silica plug to afford a pale-yellow glass, yield 830 mg (2.56 mmol, 79%). This material had purity by GC c.a. 98% and could be used in the cyclization step as is without additional purification. If desired, diastereomeric bromocyclopropanes can be additionally purified and separated by preparative column chromatography on Silica gel eluting with a CH_2Cl_2/EtOAc mixture (40:1). HRMS (TOF ES): found 346.0786, calculated for $C_{16}H_{22}BrNONa$ (M + Na) 346.0782 (1.2 ppm). Individual isomers

were isolated as colorless glass (*trans*-**180i**) and colorless crystalline solid (*cis*-**180i**), respectively. ***trans*-180i**: R_f 0.42 (CH_2Cl_2/EtOAc 40:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 4.78 (q, *J* = 17.8 Hz, 2H), 3.20 (dd, *J* = 8.2, 4.9 Hz, 1H), 1.71 (dd, *J* = 8.2, 6.7 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 9H), 0.82 (dd, *J* = 6.7, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 140.0, 128.8 (2C), 127.1, 125.9 (2C), 58.3, 49.5, 28.6 (3C), 28.5, 27.9, 22.2, 20.3. ***cis*-180i**: mp 165-166 °C; R_f 0.35 (CH_2Cl_2/EtOAc 40:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.10 (m, 5H), 5.10 (d, *J* = 18.3 Hz, 1H), 4.61 (d, *J* = 18.3 Hz, 1H), 2.95 (dd, *J* = 7.5, 4.6 Hz, 1H), 1.67 (dd, *J* = 6.7, 4.6 Hz, 1H), 1.39 (s, 9H), 1.22 (s, 3H), 1.12 (dd, *J* = 7.5, 6.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 140.8, 128.6 (2C), 126.9, 126.1 (2C), 59.0, 49.9, 30.4, 28.6 (3C), 26.9, 23.8, 22.4. EA found C 59.50, 59.03, H 7.01, 6.94, N 4.52, 4.19, calculated for $C_{16}H_{22}BrNO$: C 59.27, H 6.84; N 4.32.



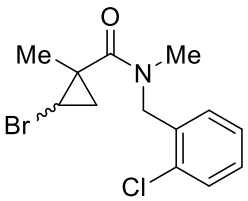
2-Bromo-N-(4-fluorobenzyl)-N,1-dimethylcyclopropane-1-carboxamide (**180j**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (340 mg, 1.72 mmol), 1-(4- fluorophenyl)-*N*-methylmethanamine (239 mg, 1.72 mmol), and triethylamine (988 μL 717 mg, 7.08 mmol). The reaction mixture was stirred at room temperature overnight. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a yellow oil (R_f 0.37). Yield: 413 mg (1.37 mmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.31–7.27 (m), 7.27–7.94 (m), ∑4H], 5.14–4.36 (m, 2H), [3.20 (dd, *J* = 8.2, 4.9 Hz), 3.10–2.85 (m), ∑4H], [1.82–1.73 (m), 1.69–1.63 (m), ∑1H], [1.49 (s), 1.42 (s), 1.35 (s), ∑3H], [1.22 (t, *J* = 7.1 Hz), 0.94 (dd, *J* = 6.7, 4.9 Hz), ∑1H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ (171.2, 170.5, 1C), [162.23 (d, $^1J_{CF}$ = 246.1 Hz), 162.19 (d, $^1J_{CF}$ = 246.0 Hz), 1C], [132.9 (d, $^4J_{CF}$

= 3.5 Hz), 132.7 (br. s), 1C], [130.0 (d, $^{3}J_{CF}$ = 8.2 Hz), 128.3 (d, $^{3}J_{CF}$ = 7.9 Hz), 2C], [115.8 (d, $^{2}J_{CF}$ = 23.5 Hz), 115.3 (d, $^{2}J_{CF}$ = 21.7 Hz), 2C], (52.7, 50.7, 1C), (35.0, 33.5, 1C), (27.8, 25.8, 1C), [27.5 (br), 26.0, 1C], (25.8, 20.9, 1C), [21.8, 18.9 (br), 1C]; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9, - 115.3; FT IR (NaCl, cm^{-1}): 2930, 2360, 2342, 1700, 1684, 1645, 1540, 1508, 1403, 1222, 1106, 924, 817, 668, 650; HRMS (TOF ES): found 322.0217, calculated for $C_{13}H_{15}BrFNONa$ (M + Na) 322.0219 (0.6 ppm); EA found C 51.98, 52.10, H 5.24, 4.82, N 4.95, 4.69, calculated for $C_{13}H_{15}BrFNO$: C 52.02, H 5.04, N 4.67.

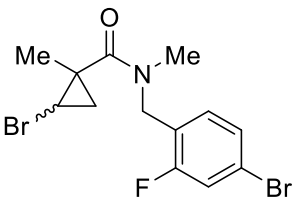


2-Bromo-N-(2,4-difluorobenzyl)-N,1-dimethylcyclopropane-1-carboxamide (**180k**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (400 mg, 2.03 mmol), 1-(2,4-difluorophenyl)-*N*-methylmethanamine (319 mg, 2.03 mmol), and triethylamine (710 μL, 515 mg, 5.09 mmol). The reaction mixture was stirred at room temperature overnight. The product was isolated by column chromatography eluting with a CH_2Cl_2/MeOH mixture (40:1) as a pale-yellow oil (R_f 0.43). Yield: 490 mg (1.54 mmol, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.44–7.39 (m), 7.36 (s), 7.27–7.17 (m), ∑1H], 6.95–6.75 (m, 2H), 5.08–4.45 (m, 2H), 3.23–2.83 (m, 4H), [1.75 (dd, *J* = 8.2, 6.6 Hz), 1.69–1.61 (m), ∑1H], [1.48 (s), 1.41 (s), 1.32 (s), ∑3 H], [1.21 (t, *J* = 7.2 Hz), 0.93 (dd, *J* = 6.7, 4.9 Hz), ∑1H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ (172.0, 170.7, 1C), [162.4 (dd, $^{1}J_{CF}$ = 249.0 Hz, $^{3}J_{CF}$ = 11.8 Hz), 162.2 (dd, $^{1}J_{CF}$ = 247.6 Hz, $^{3}J_{CF}$ = 11.9 Hz), 1C), [161.1 (dd, $^{1}J_{CF}$ = 248.2 Hz, $^{3}J_{CF}$ = 11.9 Hz), 1C], [131.8 (dd, $^{3}J_{CF}$ = 9.5 Hz, $^{3}J_{CF}$ = 5.7 Hz), 131.4 (br. s), 1C], [120.0 (dd, $^{2}J_{CF}$ = 15.0 Hz, $^{4}J_{CF}$ = 3.9 Hz), 119.9 (br. s), 1C], [111.7 (dd, $^{2}J_{CF}$ = 21.2 Hz, $^{4}J_{CF}$ = 3.9 Hz), 111.5 (dd, $^{2}J_{CF}$ = 20.8 Hz, $^{4}J_{CF}$ = 3.7 Hz), 1C], [104.3 (t, $^{2}J_{CF}$ = 25.2 Hz, $^{4}J_{CF}$ = 3.9 Hz), 103.5 (t, $^{2}J_{CF}$ = 25.5 Hz), 1C], [46.8 (d, $^{3}J_{CF}$ = 4.8

Hz), 44.2 (t, $^{3}J_{CF}$ = 3.6 Hz), 1C], (35.4, 35.1, 1C), (27.8, 27.4 (br), 1C), (25.9, 25.8, 1C), (21.80, 21.77, 1C), (20.9, 18.9, 1C); ^{19}F NMR (376 MHz, Chloroform-*d*) δ - 111.0 (d, $^{4}J_{FF}$ = 7.3 Hz), -111.1 (d, $^{4}J_{FF}$ = 7.4 Hz), -114.0 (d, $^{4}J_{FF}$ = 7.2 Hz), -115.1 (d, $^{4}J_{FF}$ = 7.4 Hz). FT IR (NaCl, cm^{-1}): 2933, 2360, 2341, 1645, 1505, 1487, 1430, 1403, 1269, 1139, 1106, 1091, 964, 850, 668, 621. HRMS (TOF ES): found 318.0309, calculated for $C_{13}H_{15}BrF_2NO$ (M + H) 318.0305 (1.3 ppm); EA found C 48.81, 49.33, H 4.64, 4.20, N 4.28, 4.32, calculated for $C_{13}H_{14}BrF_2NO$: C 49.08, H 4.44, N 4.40.

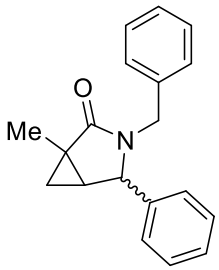


2-Bromo-N-(2-chlorobenzyl)-N,1-dimethylcyclopropane-1-carboxamide (**180l**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (494 mg, 2.50 mmol), 1-(2- chlorophenyl)-*N*-methylmethanamine (389 mg, 2.50 mmol), and triethylamine (886 μL 642 mg, 6.35 mmol). The reaction mixture was stirred at room temperature overnight. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:2) as a colorless glass (R_f 0.33). Yield: 586 mg (1.85 mmol, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.45–7.28 (m), 7.24–7.19 (m), 7.12 (br. s), ∑4H], 5.12–4.52 (m, 2H), 3.26–2.88 (m, 4H), [1.77 (br. s), 1.69–1.65 (m), 1.52 (br. s), 1.45 (s), 1.26–1.16 (m), 0.94 (br. s), ∑5H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ (171.6, 170.7, 1C), (134.4, 134.2, 1C), (133.7, 132.8, 1C), (129.5, 128.8, 128.60, 128.56, 127.23, 127.18, 127.1, 127.0, 4C), (51.3, 48.7, 1C), (35.5, 34.5, 1C), (28.0, 26.0, 1C), (25.9, 25.6, 1C), (22.5, 21.8, 21.5, 21.0, 2C); FTIR (NaCl, cm^{-1}): 2932, 1644, 1486, 1443, 1402, 1093, 1050, 752; HRMS (TOF ES): found 322.0196, calculated for $C_{13}H_{15}BrClNOLi$ (M + Li) 322.0186 (3.1 ppm); EA found C 49.55, 49.04, H 4.64, 5.05, N 4.57, 4.30, calculated for $C_{13}H_{15}BrClNO$: C 49.32, H 4.78, N 4.42.



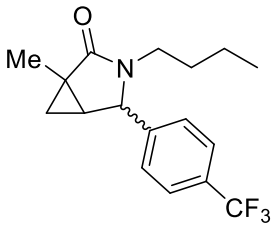
2-Bromo-N-(4-bromo-2-fluorobenzyl)-N,1-dimethylcyclopropane-1-carboxamide (**180m**). This compound was synthesized according to Typical procedure employing 2-bromo-1-methylcyclopropane-1-carbonyl chloride (494 mg, 2.50 mmol), 1-(4-bromo-2-fluorophenyl)-*N*-methylmethanamine (545 mg, 2.50 mmol), and triethylamine (886 μL 642 mg, 6.35 mmol). The reaction mixture was stirred at room temperature overnight. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:2) as a pale-yellow oil (R_f 0.23). Yield: 853 mg (2.25 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.36–7.27 (m), 7.28–7.08 (m), ∑3H], 5.05–4.47 (m, 2H), 3.21–2.86 (m, 4H), [1.75 (dd, *J* = 8.2, 6.7 Hz), 1.64 (dd, *J* = 6.9, 4.7 Hz), ∑1H], [1.48 (s), 1.41 (s), 1.30 (s), ∑3H], [1.21 (t, *J* = 7.1 Hz), 0.93 (dd, *J* = 6.7, 4.9 Hz), ∑1H]; ^{13}C NMR (126 MHz, $CDCl_3$) δ [172.0, 170.8, 1C], 160.8 (d, $^{1}J_{CF}$ = 250.8 Hz, 1C), [131.9 (d, $^{3}J_{CF}$ = 4.6 Hz), 131.5 (br. s), 1C], [127.9 (d, $^{4}J_{CF}$ = 3.4 Hz), 127.7 (d, $^{4}J_{CF}$ = 3.6 Hz), 1C], [123.3 (d, $^{2}J_{CF}$ = 15.2 Hz), 123.1 (br. s), 1C], [121.7 (br. s), 121.4 (d, $^{3}J_{CF}$ = 9.2 Hz), 1C], [119.2 (br. s), 118.8 (d, $^{2}J_{CF}$ = 22.4 Hz), 1C], [47.0 (br. s), 44.3 (d, $^{3}J_{CF}$ = 3.7 Hz), 1C], (35.5, 35.2, 1C), (27.8, 27.3, 1C), (25.9, 25.8, 1C), (21.79, 21.76, 1C), (20.9, 18.9, 1C); ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.3, -116.4; FT IR (NaCl, cm^{-1}): 2932, 1644, 1605, 1484, 1401, 1218, 1103, 875, 814, 611; HRMS (TOF ES): found 399.9341, calculated for $C_{13}H_{14}Br_2FNONa$ (M + Na) 399.9324 (4.3 ppm); EA found C 41.48, 41.39, H 3.52, 3.61, N 3.56, 3.76, calculated for $C_{13}H_{14}Br_2FNO$: C 41.19, H 3.72, N 3.70.

3.5.3 Cyclization of bromocyclopropanes



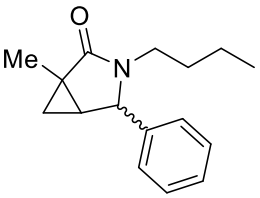
(1R*,5S*)-3-Benzyl-1-methyl-4-phenyl-3-azabicyclo[3.1.0]hexan2-one (**182a**). Typical procedure: an oven-dried Wheaton vial equipped with a Teflon septum cap was charged with freshly sublimed *t*-BuOK (315 mg, 2.80 mmol) and 18-crown-6 ether (18.5 mg, 0.07 mmol) in a nitrogen-filled glovebox. Anhydrous THF (2.22 mL) was then added to this vial and the solution was stirred to premix for 30 minutes. A solution of *N*,*N*-dibenzyl-2-bromo-1-methylcyclopropane-1-carboxamide (**180a**) (251 mg, 0.70 mmol) in anhydrous THF (1.48 mL) was added dropwise to the stirred reaction mixture, which was then stirred at 30 °C until starting materials were consumed (10 min for the reaction of **182a**). The reaction was then quenched by pouring the mixture into brine (35 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried with $MgSO_4$, gravity filtered, and concentrated in *vacuo*. The crude material contains a mixture of diastereomers 45 : 55 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (2 : 1) afforded the titled product as a pale yellow oil (R_f 0.38). Yield 156 mg (0.56 mmol, 80%). *endo*-**182a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (m, 3H), 7.31–7.21 (m, 3H), 7.20–7.14 (m, 2H), 7.09–7.01 (m, 2H), 5.06 (d, *J* = 15.0 Hz, 1H), 4.57 (d, *J* = 6.0 Hz, 1H), 3.50 (d, *J* = 14.5 Hz, 1H), 1.93–1.86 (m, 1H), 1.42 (s, 3H), 1.05 (t, *J* = 4.5 Hz, 1H), 0.64 (dd, *J* = 7.8, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 138.5, 136.6, 128.9 (2C), 128.9 (2C), 128.7 (2C), 128.0, 127.6, 127.0 (2C), 59.6, 44.2, 27.1, 26.6, 16.4, 15.2. *exo*-**182a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (m, 3H), 7.31–7.21 (m, 3H), 7.20–7.14 (m, 2H), 7.09–7.01 (m, 2H), 5.00 (d, *J* = 14.9 Hz, 1H), 4.12 (s, 1H), 3.36 (d, *J* = 14.7 Hz, 1H), 1.58 (dd, *J* = 7.5, 3.9 Hz, 1H), 1.48 (s, 3H), 0.72 (t, *J* = 4.3 Hz, 1H), 0.92 (dd, *J* = 7.5, 4.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 140.8, 137.2, 129.2 (2C), 128.8 (2C), 128.5, 128.5 (2C), 127.6, 127.0 (2C), 61.8, 43.9, 26.4, 25.6, 19.3, 15.1. FTIR (NaCl, cm^{-1}): 3063, 3030, 2961, 2928,

2869, 1694, 1495, 1454, 1414, 1357, 1301, 1200, 1151, 1078, 1029, 941, 747, 761, 701, 622; HRMS (TOF ES): found 300.1378, calculated for $C_{19}H_{19}NONa$ (M + Na) 300.1364 (4.7 ppm); EA found C 82.12, 82.00, H 6.76, 6.74, N 5.19, 5.12, calculated for $C_{19}H_{19}NO$: C 82.28, H 6.90, N 5.05.



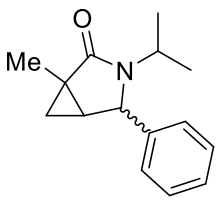
(1R*,5S*)-3-Butyl-1-methyl-4-(4-(trifluoromethyl)phenyl)-3azabicyclo[3.1.0]hexan-2-one (**182d**). This compound was synthesized according to the Typical procedure employing 2-bromo-*N*-butyl-1-methyl-*N*-(4(trifluoromethyl)benzyl)cyclopropane-1-carboxamide (**180d**) (67 mg, 0.171 mmol), 18-crown-6 ether (4.5 mg, 0.017 mmol), and *t*-BuOK (77 mg, 0.68 mmol). The reaction mixture was stirred at rt for 5 min and then quenched with a saturated solution of ammonium chloride. The crude material contains an inseparable mixture of diastereomers 15 : 85 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (2 : 1) afforded the titled product as a colorless oil (R_f 0.33). Yield: 12.4 mg (0.046 mmol, 27%). *endo*-**182d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 4.90 (d, *J* = 6.2 Hz, 1H), 3.66 (ddd, *J* = 13.9, 8.9, 7.1 Hz, 1H), 2.50–2.43 (m, 1H), 1.96 (ddd, *J* = 7.7, 6.1, 4.0 Hz, 1H), 1.41 (s, 3H), 1.36–1.25 (m, 2H), 1.25–1.15 (m, 2H), 0.89 (t, *J* = 4.5 Hz, 1H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.62 (dd, *J* = 7.8, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2, 143.0, 130.0 (q, $^2J_{CF}$ = 40.0 Hz), 126.9 (2C), 125.8 (q, $^3J_{CF}$ = 3.7 Hz, 2C), 124.0 (q, $^1J_{CF}$ = 271.9 Hz), 59.7, 40.2, 28.8, 28.2, 26.6, 20.1, 16.1, 15.0, 13.8. *exo*-**182d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.43 (s, 1H), 3.59 (dt, *J* = 14.0, 7.8 Hz, 1H), 2.46 (ddd, *J* = 13.8, 7.8, 5.5 Hz, 1H), 1.57 (dd, *J* = 7.5, 4.0 Hz, 1H), 1.43 (s, 3H), 1.36–1.25 (m, 2H), 1.25–1.15 (m, 2H), 1.00 (dd, *J* = 7.5, 4.7 Hz, 1H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.80 (t, *J* = 4.3 Hz, 1H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 176.5, 145.4, 130.6 (q, $^2J_{CF}$ = 32.7 Hz), 126.9 (2C), 126.1 (q, $^3J_{CF}$ = 3.9 Hz, 2C), 124.0 (q, $^1J_{CF}$ = 271.9 Hz), 62.2, 40.0, 29.6, 26.4, 25.8, 19.9, 19.9, 14.9, 13.7. ^{19}F NMR (376 MHz, chloroform-d) δ −62.5, −62.6; FTIR (NaCl, cm^{-1}): 2961, 2933, 2873, 1676, 1645, 1459, 1414, 1326, 1294, 1246, 1166, 1125, 1067, 1018, 959, 846, 756, 608; HRMS (TOF ES): found 312.1578, calculated for $C_{17}H_{21}NOF_3$ (M + H) 312.1575 (1.0 ppm); EA found C 65.70, 65.45, H 6.38, 6.65, N 4.39, 4.78, calculated for $C_{17}H_{20}F_3NO$: C 65.58, H 6.48, N 4.50.



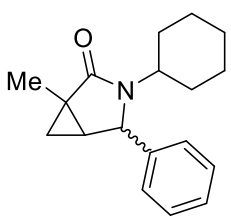
(1R*,5S*)-3-Butyl-1-methyl-4-phenyl-3-azabicyclo[3.1.0]hexan-2-one (**182f**). This compound was synthesized according to the Typical procedure employing *N*-benzyl-2-bromo-*N*-butyl-1-methylcyclopropane-1-carboxamide (**180f**) (229 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred overnight at 30 °C. The crude material contains an inseparable mixture of diastereomers 53 : 47 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (3 : 1) afforded the titled product as a yellow oil (R_f 0.30). Yield 119.2 mg (0.49 mmol, 70%). *endo*-**182f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 3H), 7.15–7.09 (m, 2H), 4.85 (d, *J* = 6.0 Hz, 1H), 3.63 (ddd, *J* = 13.8, 8.6, 7.3 Hz, 1H), 2.50 (m, 1H), 1.93 (ddd, *J* = 7.7, 6.0, 3.9 Hz, 1H), 1.40 (s, 3H), 1.38–1.12 (m, 4H), 0.99–0.91 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H), 0.59 (dd, *J* = 7.7, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 138.8, 128.8 (2C), 127.9, 126.8 (2C), 60.2, 40.2, 29.0, 26.9, 26.7, 20.2, 16.2, 15.2, 13.9. *exo*-**182f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 3H), 7.22–7.17 (m, 2H), 4.35 (s, 1H), 3.55 (dt, *J* = 13.9, 7.7 Hz, 1H), 2.50 (m, 1H), 1.59 (dd, *J* = 7.5, 3.9 Hz, 1H), 1.42 (s, 3H), 1.38–1.12 (m, 4H), 0.99–0.91 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H), 0.76 (t, *J* = 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 141.3, 129.1 (2C), 128.3, 126.7 (2C), 62.8, 39.9, 29.8, 26.7, 25.9, 20.0 (2C), 15.1,

13.8. FTIR (NaCl, cm^{-1}): 2960, 2931, 2872, 1692, 1457, 1417, 1372, 1219, 1051, 756, 701. HRMS (TOF ES): found 266.1514, calculated for $C_{16}H_{21}NONa$ (M + Na) 266.1521 (2.6 ppm); EA found C 78.81, 79.23, H 8.42, 8.50, N 5.92, 5.55, calculated for $C_{16}H_{21}NO$: C 78.97, H 8.70, N 5.76.

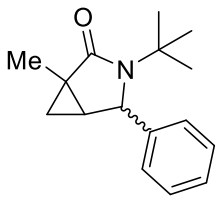


(1R*,5S*)-3-Isopropyl-1-methyl-4-phenyl-3-azabicyclo[3.1.0]hexan-2-one (**182g**). This compound was synthesized according to the Typical procedure employing *N*-benzyl-2-bromo-*N*-isopropyl-1-methylcyclopropane-1-carboxamide (**180g**) (217 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred at 30 °C for 3 h. The crude material contains a mixture of diastereomers 50 : 50 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (3 : 1) afforded the titled product as a pale yellow glass (R_f 0.36, 0.30). Yield 104.3 mg (0.455 mmol, 65%). Analytical samples of individual diastereomers were obtained by column chromatography on silica gel eluting with a CH_2Cl_2/EtOAc mixture (10 : 1). *endo*-**182g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (m, 3H), 7.26–7.21 (m, 2H), 4.86 (d, *J* = 5.8 Hz, 1H), 3.47 (p, *J* = 6.8 Hz, 1H), 1.91 (ddd, *J* = 7.7, 5.9, 3.9 Hz, 1H), 1.38 (s, 3H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.08 (t, *J* = 4.4 Hz, 1H), 0.62 (dd, *J* = 7.7, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.2, 140.4, 128.7 (2C), 128.0, 126.9 (2C), 61.4, 46.1, 27.3, 26.8, 20.0, 19.6, 16.2, 15.1. *exo*-**182g**: ^{1}H NMR (500 MHz, $CDCl_3$), δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.33–7.28 (m, 1H), 7.27–7.21 (m, 2H), 4.36 (s, 1H), 4.02 (p, *J* = 6.9 Hz, 1H), 1.49 (dd, *J* = 7.3, 3.9 Hz, 1H), 1.44 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.91 (dd, *J* = 7.3, 4.6 Hz, 1H), 0.77 (d, *J* = 6.9 Hz, 3H), 0.66 (t, *J* = 4.2 Hz, 1H); ^{13}C NMR (126 MHz, CDCl3) δ 176.8, 143.6, 128.9 (2C), 128.2, 126.7 (2C), 61.5, 44.7, 26.6, 26.2, 21.3, 20.4, 19.5, 15.0. FTIR (NaCl, cm^{-1}): 2970, 2931, 1685, 1456, 1412, 1380, 1345, 1223, 1028, 956, 763, 738, 702. HRMS (TOF ES):

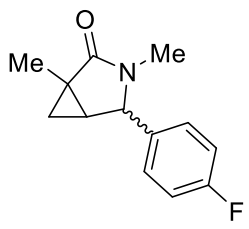
found 252.1353, calculated for $C_{15}H_{19}NONa$ (M + Na) 252.1364 (4.4 ppm); EA found C 78.47, 78.68, H 8.55, 8.18, N 6.07, 6.40, calculated for $C_{15}H_{19}NO$: C 78.56, H 8.35, N 6.11.



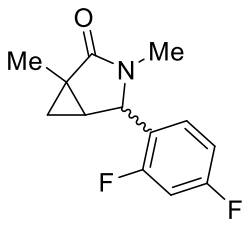
(1R*,5S*)-3-Cyclohexyl-1-methyl-4-phenyl-3-azabicyclo[3.1.0]hexan-2-one (**182h**). This compound was synthesized according to the Typical procedure employing *N*-benzyl-2-bromo-*N*-cyclohexyl-1-methylcyclopropane-1-carboxamide (**180h**) (245 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred overnight at 30 °C. The crude material contains an inseparable mixture of diastereomers 45 : 55 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (3 : 1) afforded the titled product as a colorless glass (R_f 0.38). Yield 141.3 mg (0.525 mmol, 75%). *endo*-**182h** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (m, 3H), 7.25–7.18 (m, 2H), 4.85 (d, *J* = 6.0 Hz, 1H), 3.10 (tt, *J* = 12.2, 3.5 Hz, 1H), 2.04–1.90 (m, 1H), 1.87 (ddd, *J* = 7.8, 6.0, 3.9 Hz, 1H), 1.67 (dd, *J* = 22.8, 11.2 Hz, 4H), 1.57–1.44 (m, 2H), 1.35 (s, 3H), 1.17–0.92 (m, 4H), 0.57 (dd, *J* = 7.8, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.2, 140.6, 128.6 (2C), 127.9, 126.8 (2C), 61.2, 54.5, 30.1, 29.6, 27.5, 26.8, 26.3, 26.0, 25.5, 16.2, 15.1. *exo*-**182h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (m, 3H), 7.25–7.18 (m, 2H), 4.37 (s, 1H), 3.65 (tt, *J* = 12.1, 3.8 Hz, 1H), 1.73–1.59 (m, 1H), 1.55–1.42 (m, 5H), 1.42 (s, 3H), 1.43–1.33 (m, 1H), 1.30–1.21 (m, 2H), 1.18–1.00 (m, 1H), 1.00–0.70 (m, 2H), 0.64 (t, *J* = 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 143.9, 128.9 (2C), 128.0, 126.6 (2C), 61.6, 52.7, 31.9, 30.9, 26.8, 26.3, 25.9, 25.9, 25.5, 19.6, 15.0. FTIR (NaCl, cm^{-1}): 2931, 2855, 1684, 1453, 1414, 1360, 1205, 1028, 894, 751, 736, 702, 624. HRMS (TOF ES): found 292.1664, calculated for $C_{18}H_{23}NONa$ (M + Na) 292.1677 (4.4 ppm); EA found C 80.31, 80.34, H 8.89, 8.86, N 4.95, 5.14, calculated for $C_{18}H_{23}NO$: C 80.26, H 8.61, N 5.20.



(1R*,5S*)-3-(tert-Butyl)-1-methyl-4-phenyl-3-azabicyclo[3.1.0]hexan-2-one (**182i**). This compound was synthesized according to the Typical procedure employing *N*-benzyl-2-bromo-*N*-(*tert*-butyl)-1-methylcyclopropane-1-carboxamide (**180i**) (227 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred overnight at 30 °C. The crude material contains an inseparable mixture of diastereomers 47 : 53 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (3 : 1) afforded the titled product as a colorless glass (R_f 0.44). Yield 109 mg (0.448 mmol, 64%). *endo*-**182i**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 4H), 7.28–7.14 (m, 1H), 4.97 (d, *J* = 6.5 Hz, 1H), 1.88 (ddd, *J* = 7.9, 6.5, 3.7 Hz, 1H), 1.34 (s, 3H), 1.26 (s, 9H), 0.98 (t, *J* = 4.3 Hz, 1H), 0.49 (dd, *J* = 7.9, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.8, 144.7, 128.5 (2C), 127.1, 125.5 (2C), 61.1, 54.4, 28.3 (3C), 28.3, 28.3, 16.1, 15.7. *exo*-**182i**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 4H), 7.28–7.14 (m, 1H), 4.57 (s, 1H), 1.40 (dd, *J* = 7.2, 3.9 Hz, 1H), 1.38 (s, 3H), 1.24 (s, 9H), 0.84 (dd, *J* = 7.2, 4.3 Hz, 1H), 0.66 (t, *J* = 4.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 143.7, 128.9 (2C), 127.7, 126.1 (2C), 62.7, 55.5, 28.1 (3C), 26.4, 26.0, 19.2, 14.9. FTIR (NaCl, cm^{-1}): 2963, 2929, 2869, 1664, 1493, 1455, 1396, 1383, 1359, 1343, 1221, 1198, 1141, 950, 762, 740, 705; HRMS (TOF ES): found 266.1528, calculated for $C_{16}H_{21}NONa$ (M + Na) 266.1521 (2.6 ppm); EA found C 79.05, 79.07, H 8.60, 8.95, N 5.92, 5.57, calculated for $C_{16}H_{21}NO$: C 78.97, H 8.70, N 5.76.

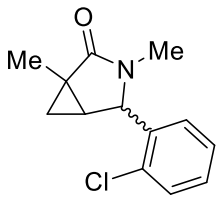


(1R*,5S*)-4-(4-Fluorophenyl)-1,3-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (**182j**). This compound was synthesized according to the Typical procedure employing 2-bromo-*N*-(4-fluorobenzyl)-*N*,1-dimethylcyclopropane-1-carboxamide (**180j**) (51 mg, 0.171 mmol), 18-crown-6 ether (4.5 mg, 0.017 mmol), and *t*-BuOK (76 mg, 0.68 mmol). The reaction mixture was stirred at rt for 4 h. The crude material contains an inseparable mixture of diastereomers 60 : 40 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (3 : 1) afforded the titled product as a colorless glass (R_f 0.36). Yield 21.6 mg (0.099 mmol, 58%). *endo*-**182j**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.02 (m, 4H), 4.68 (d, *J* = 5.9 Hz, 1H), 2.61 (s, 3H), 1.93 (ddd, *J* = 7.7, 5.9, 4.0 Hz, 1H), 1.40 (s, 3H), 0.90 (t, *J* = 4.6 Hz, 1H), 0.63 (dd, *J* = 7.8, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 162.4 (d, $^1J_{CF}$ = 246.1 Hz), 136.5 (d, $^4J_{CF}$ = 3.5 Hz), 128.0 (d, $^3J_{CF}$ = 8.1 Hz, 2C), 115.7 (d, $^2J_{CF}$ = 21.2 Hz, 2C), 62.2, 28.1, 26.9, 25.7, 16.3, 14.9. *exo*-**182j**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.13 (m, 2H), 7.11–7.02 (m, 2H), 4.23 (s, 1H), 2.57 (s, 3H), 1.57 (dd, *J* = 7.6, 3.9 Hz, 1H), 1.42 (s, 3H), 0.96 (dd, *J* = 7.6, 4.7 Hz, 1H), 0.81 (t, *J* = 4.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 162.6 (d, $^1J_{CF}$ = 247.0 Hz), 136.5 (d, $^4J_{CF}$ = 3.5 Hz), 128.1 (d, $^3J_{CF}$ = 8.2 Hz, 2C), 116.0 (d, $^2J_{CF}$ = 21.7 Hz, 2C), 64.5, 27.9, 26.6, 25.7, 20.0, 15.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ−113.8, −114.6; FTIR (NaCl, cm^{-1}): 2929, 1683, 1509, 1481, 1398, 1223, 1158, 1007, 845, 819, 752, 668, 647. HRMS (TOF ES): found 242.0960, calculated for $C_{13}H_{14}NOFNa$ (M + Na) 242.0957 (1.2 ppm); EA found C 71.35, 71.27, H 6.18, 6.34, N 6.26, 6.33, calculated for $C_{13}H_{14}FNO$: C 71.21, H 6.44, N 6.39. Slow crystallization of the purified material from hexane afforded a crop of crystals of *exo*-**182j** suitable for X-ray analysis (CCDC #1575277).

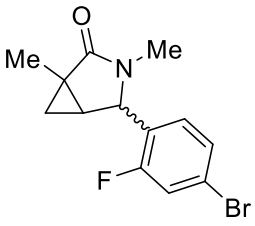


(1R*,5S*)-4-(2,4-Difluorophenyl)-1,3-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (**182k**). This compound was synthesized according to the Typical procedure employing 2-bromo-*N*-(2,4-difluorobenzyl)-*N*,1-dimethylcyclopropane-1-carboxamide (**180k**) (54 mg, 0.171 mmol), 18-crown-6 ether (4.5 mg, 0.017 mmol), and *t*-BuOK (76 mg, 0.68 mmol). The reaction mixture was stirred at rt for 5 min and then quenched with a saturated solution of ammonium chloride. The crude material contains an inseparable mixture of diastereomers 69 : 31 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (2 : 3) afforded the titled product as a colorless oil (R_f 0.38). Yield 30.2 mg (0.127 mmol, 75%). *endo*-**182k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93–6.79 (m, 3H), 4.95 (d, *J* = 5.9 Hz, 1H), 2.64 (s, 3H), 2.06 (ddd, *J* = 7.8, 5.9, 4.0 Hz, 1H), 1.38 (s, 3H), 0.77 (t, *J* = 4.5 Hz, 1H), 0.64 (dd, *J* = 7.8, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 162.3 (dd, $^{1}J_{CF}$ = 249.2 Hz, $^{3}J_{CF}$ = 13.2 Hz), 160.7 (dd, $^{1}J_{CF}$ = 248.8 Hz, $^{3}J_{CF}$ = 12.0 Hz), 127.8 (dd, $^{3}J_{CF}$ = 9.4 Hz, $^{3}J_{CF}$ = 5.8 Hz), 122.1 (dd, $^{2}J_{CF}$ = 13.2 Hz, $^{4}J_{CF}$ = 3.9 Hz), 111.3 (dd, $^{2}J_{CF}$ = 21.0 Hz, $^{4}J_{CF}$ = 3.6 Hz), 104.3 (t, $^{2}J_{CF}$ = 25.5 Hz), 56.0 (d, $^{3}J_{CF}$ = 4.5 Hz), 28.5, 26.5, 25.6, 16.5, 14.9. *exo*-**182k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14–7.07 (m, 1H), 6.93–6.79 (m, 2H), 4.57 (s, 1H), 2.59 (s, 3H), 1.60 (dd, *J* = 7.6, 3.9 Hz, 1H), 1.40 (s, 3H), 0.98 (dd, *J* = 7.5, 4.7 Hz, 1H), 0.82 (t, *J* = 4.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 162.7 (dd, $^{1}J_{CF}$ = 249.7 Hz, $^{3}J_{CF}$ = 12.2 Hz), 160.8 (dd, $^{1}J_{CF}$ = 249.7 Hz, $^{3}J_{CF}$ = 12.2 Hz), 128.8 (dd, $^{3}J_{CF}$ = 9.9 Hz, $^{3}J_{CF}$ = 5.5 Hz), 123.5 (dd, $^{2}J_{CF}$ = 13.2 Hz, J_{CF} = 3.9 Hz), 112.0 (dd, J_{CF} = 21.0 Hz, J_{CF} = 3.7 Hz), 104.4 (t, $^{2}J_{CF}$ = 25.5 Hz), 58.2 (d, $^{3}J_{CF}$ = 3.5 Hz), 27.9, 25.7, 25.6, 20.0, 14.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.9 (d, $^{4}J_{FF}$ = 7.5 Hz), −111.1 (d, $^{4}J_{FF}$ = 7.3 Hz), −115.97 (d, $^{4}J_{FF}$ = 7.8 Hz), −116.03 (d, $^{4}J_{FF}$ = 7.3 Hz); FTIR (NaCl, cm^{-1}): 2932, 1694, 1617, 1503, 1430, 1397, 1269, 1234, 1140, 1092, 974, 961, 850, 765, 610. HRMS (TOF ES): found 260.0862, calculated for $C_{13}H_{13}NOF_2Na$ (M + Na)

260.0863 (0.4 ppm); EA found C 65.92, 65.51, H 5.60, 5.67, N 6.14, 5.82, calculated for $C_{13}H_{13}F_2NO$: C 65.81, H 5.52, N 5.90.

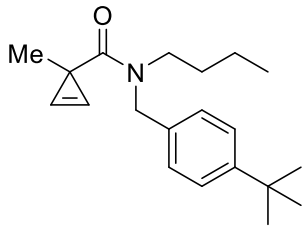


(1R*,5S*)-4-(2-Chlorophenyl)-1,3-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (**182l**). This compound was synthesized according to the Typical procedure employing 2-bromo-*N*-(2-chlorobenzyl)-*N*,1-dimethylcyclopropane-1-carboxamide (**180l**) (54 mg, 0.171 mmol), 18-crown-6 ether (4.5 mg, 0.017 mmol), and *t*-BuOK (77 mg, 0.68 mmol). The reaction mixture was stirred at rt for 2 min and then quenched with a saturated solution of ammonium chloride. The crude material contains an inseparable mixture of diastereomers 70 : 30 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/EtOAc (2 : 3) afforded the titled product as a colorless oil (R_f 0.45). Yield 27.7 mg (0.118 mmol, 69%). *endo*-**182l**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.39 (m, 1H), 7.33–7.22 (m, 2H), 6.86 (dd, *J* = 6.9, 2.4 Hz, 1H), 5.07 (d, *J* = 5.9 Hz, 1H), 2.67 (s, 3H), 2.24 (ddd, *J* = 7.8, 5.9, 4.0 Hz, 1H), 1.41 (s, 3H), 0.75 (t, *J* = 4.5 Hz, 1H), 0.60 (dd, *J* = 7.8, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.3, 136.4, 133.1, 130.2, 128.8, 127.1, 127.0, 59.9, 28.8, 26.6, 24.9, 16.5, 15.2. *exo*-**182l**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.39 (m, 1H), 7.33–7.22 (m, 2H), 7.11 (dd, *J* = 7.3, 2.1 Hz, 1H), 4.80 (s, 1H), 2.64 (s, 3H), 1.60 (dd, *J* = 7.5, 4.0 Hz, 1H), 1.38 (s, 3H), 0.99 (dd, *J* = 7.5, 4.7 Hz, 1H), 0.86 (t, *J* = 4.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 138.0, 133.1, 130.2, 129.3, 127.7, 127.0, 61.3, 28.4, 25.2, 26.0, 20.1, 15.1. FTIR (NaCl, cm^{-1}): 2929, 1698, 1471, 1445, 1395, 1384, 1340, 1232, 1035, 972, 757, 698; HRMS (TOF ES): found 258.0660, calculated for $C_{13}H_{14}NOClNa$ (M + Na) 258.0662 (0.8 ppm); EA found C 66.21, 66.16, H 5.92, 6.10, N 5.64, 6.22, calculated for $C_{13}H_{14}ClNO$: C 66.24, H 5.99, N 5.94.

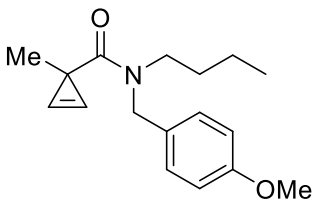


(1R*,5S*)-4-(4-Bromo-2-fluorophenyl)-1,3-dimethyl-3-azabicyclo[3.1.0]hexan-2-one (**182m**). This compound was synthesized according to the Typical procedure employing 2-bromo-*N*-(4-bromo-2-fluorobenzyl)-*N*,1-dimethylcyclopropane-1-carboxamide (**180m**) (65 mg, 0.171 mmol), 18-crown-6 ether (4.5 mg, 0.017 mmol), and *t*-BuOK (77 mg, 0.69 mmol). The reaction mixture was stirred at rt for 2 min and then quenched with a saturated solution of ammonium chloride. The crude material contains an inseparable mixture of diastereomers 72 : 28 (*endo* : *exo*). Purification by column chromatography eluting with a mixture of hexanes/ EtOAc (1 : 1) afforded the titled product as a colorless oil (R_f 0.35). Yield 37.8 mg (0.127 mmol, 74%). *endo*-**182m**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (m, 2H), 6.74 (t, *J* = 8.2 Hz, 1H), 4.89 (d, *J* = 5.9 Hz, 1H), 2.60 (s, 3H), 2.03 (ddd, *J* = 8.0, 5.8, 3.9 Hz, 1H), 1.34 (s, 3H), 0.71 (t, *J* = 4.5 Hz, 1H), 0.60 (dd, *J* = 7.8, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 160.5 (d, *J* = 250.9 Hz), 128.2 (d, *J* = 4.7 Hz), 127.7 (d, *J* = 3.6 Hz), 125.6 (d, *J* = 12.8 Hz), 121.6 (d, *J* = 9.9 Hz), 119.6 (d, *J* = 24.5 Hz), 56.2 (d, *J* = 4.4 Hz), 28.6, 26.7, 25.5, 16.6, 15.0. *exo*-**182m**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (m, 2H), 6.96 (t, *J* = 8.0 Hz, 1H), 4.52 (s, 1H), 2.56 (s, 3H), 1.55 (dd, *J* = 7.5, 3.9 Hz, 1H), 1.35 (s, 3H), 0.95 (dd, *J* = 7.5, 4.8 Hz, 1H), 0.78 (t, *J* = 4.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 160.6 (d, *J* = 253.3 Hz), 129.0 (d, *J* = 5.1 Hz), 128.3 (d, *J* = 4.7 Hz), 126.9 (d, *J* = 13.0 Hz), 122.3 (d, *J* = 9.8 Hz), 119.8 (d, *J* = 23.9 Hz), 58.3 (d, *J* = 3.6 Hz), 28.1, 25.8, 25.6, 20.1, 14.9. ^{19}F NMR (376 MHz, chloroform-d) δ −116.4, −117.3; FTIR (NaCl, cm^{-1}): 2961, 2930, 1695, 1605, 1574, 1483, 1396, 1220, 1077, 973, 883, 850, 757. HRMS (TOF ES): found 320.0056, calculated for $C_{13}H_{13}NOFBrNa$ (M + Na) 320.0062 (1.9 ppm); EA found 52.21, 52.44, H 4.29, 4.57, N 4.90, 4.64, calculated for $C_{13}H_{13}BrFNO$: C 52.37, H 4.40, N 4.70.

3.5.4 Syntheses of cyclopropenes



N-Butyl-N-(4-(tert-butyl)benzyl)-1-methylcycloprop-2-ene-1-carboxamide (**185b**). This compound was synthesized according to the Typical procedure employing 2-bromo-*N*-butyl-*N*-(4-(*tert*-butyl)benzyl)-1-methylcyclopropane-1-carboxamide (**180b**) (266 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred at 25 °C for 47 h. The product was isolated by column chromatography eluting with a mixture of hexanes/EtOAc (3 : 2) as a yellow oil (R_f 0.39). Yield 72.2 mg (0.315 mmol, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (br. s, 3H), 7.22 (br. s, 1H), 7.08 (br. s, 2H), 4.81–4.48 (m, 2H), 3.44–3.18 (m, 2H), [1.95 (br. s), 1.53–1.35 (m), ∑5H], 1.37 (br. s, 11H), 1.31 (br. s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, (150.4, 149.9, 1C), (134.6, 134.2, 1C), (127.4, 126.5, 2C), 125.6 (2C), 115.8 (2C), (50.3, 44.0, 1C), 46.4, 34.5, 31.4 (3C), (30.6, 29.1, 1C), 24.1, 23.2, 20.1, 13.9; FTIR (NaCl, cm^{-1}): 2960, 2869, 1625, 1514, 1463, 1410, 1365, 1269, 1104, 1005, 927, 819, 732, 617; HRMS (TOF ES): found 322.2147, calculated for $C_{20}H_{29}NONa$ (M + Na) 322.2147 (0.0 ppm); EA found C 80.07, 80.50, H 9.75, 9.95, N 4.93, 4.97, calculated for $C_{20}H_{29}NO$: C 80.22, H 9.76, N 4.68.



N-Butyl-N-(4-methoxybenzyl)-1-methylcycloprop-2-ene-1-carboxamide (**185c**). This compound was synthesized according to the Typical procedure employing 2-bromo-*N*-butyl-*N*-(4-methoxybenzyl)-1-methylcyclopropane-1-carboxamide (**180c**) (248 mg, 0.70 mmol), 18-crown-6 ether (18.5 mg, 0.07 mmol), and *t*-BuOK (314 mg, 2.80 mmol). The reaction mixture was stirred at 25 °C for 27

h. The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (1 : 1) as a yellow oil (R_f 0.39). Yield 105.3 mg (0.385 mmol, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ [7.30 (br. s), 7.24 (br. s), 7.07 (br. s), ∑4H], 6.86 (br. s, 2H), 4.75–4.46 (m, 2H), 3.79 (s, 3H), 3.41–3.16 (m, 2H), [1.47 (br. s), 1.37 (s), 1.26 (br. s), ∑7H], 0.90 (br. s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 158.9, 129.1, 128.0, 115.8, 114.04 (2C), 55.3, 50.1, 46.1, 43.8, 30.5, 29.0, 24.0, 23.2, 20.1, 13.9; FTIR (NaCl, cm^{-1}): 2958, 2933, 2872, 1615, 1513, 1464, 1417, 1302, 1247, 1175, 1104, 1033, 815, 621. HRMS (TOF ES): found 296.1637, calculated for $C_{17}H_{23}NO_2Na$ (M + Na) 296.1626 (3.7 ppm); EA found C 74.72, 74.89, H 8.75, 8.39, N 4.89, 5.19, calculated for $C_{17}H_{23}NO_2$: C 74.69, H 8.48, N 5.12.

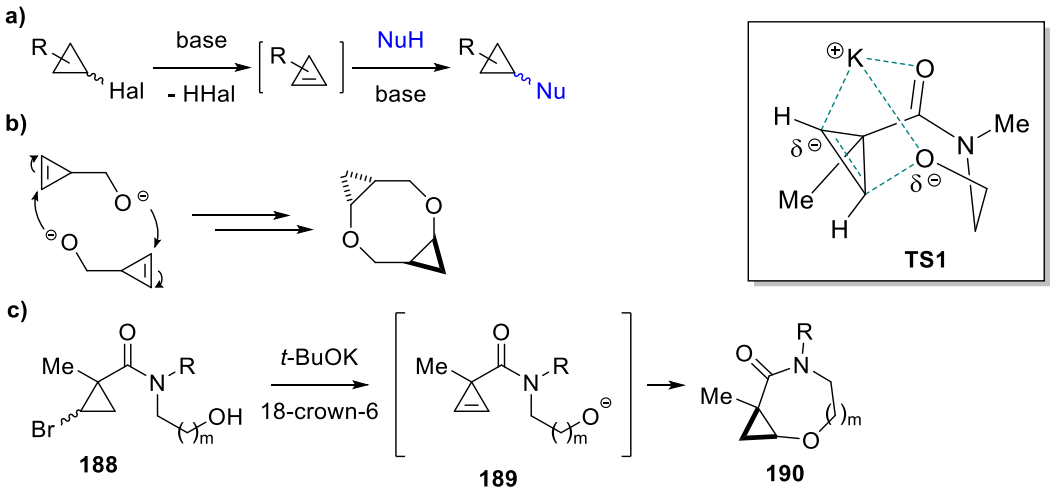
Chapter 4. Intramolecular nucleophilic addition of tethered alkoxides to cyclopropenes

4.1 Introduction

The cyclopropene double bond is characterized by enhanced strain energy and much greater electrophilicity as compared to normal olefins. This feature allows for the utilization of strain-release driven addition of various nucleophilic entities across the C=C bond of cyclopropenes.

Advances in base-assisted additions of heteroatom-based nucleophiles to cyclopropenes provided access to novel stereodefined cyclopropyl scaffolds,[116] possessing oxygen,[111,114,119] nitrogen,[107,114,120] sulfur,[121] Both intermolecular (Scheme 54a and Scheme 54b) and intramolecular (Scheme 54c) diastereoselective addition of achiral tethered oxygen-based nucleophiles affording racemic products has been reported.[123a,133]

Scheme 54



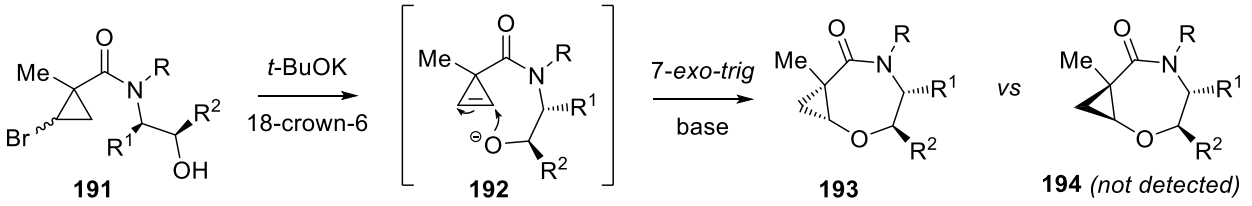
In previously published work from our group an efficient synthesis of medium cyclic ethers **190** via a formal nucleophilic cyclization of bromocyclopropanes **188** (Scheme 54c),[133a] was

described. This reaction proceeds through an in-situ base-assisted generation of reactive cyclopropene **189**, which, once formed, is immediately trapped by a tethered alkoxide. Computational studies suggested that the mechanism of this strain-release-driven reaction involves a transition state where the potassium ion is coordinated to both alkoxide and amide oxygen, as well as to the carbon atom bearing a partial negative charge (C-8) (**TS1** in Scheme 54).

It was expected and confirmed experimentally that the templating effect induced constraints on the rotors in the tether, making the cyclization pathway more favorable compared to oligo- and polymerization. Furthermore, the rigidity of such activated complexes allowed for high diastereoselectivity of the newly formed stereogenic centers when chiral amino alcohol-tethered prochiral cyclopropenes are used as substrates.

Intramolecular nucleophilic addition of tethered chiral alkoxides to prochiral cyclopropene moieties has not been fully explored. To date, only two examples were communicated by our group,[111c] using cyclopropene **192** generated in situ via 1,2-elimination of bromocyclopropane **191** (Scheme 55). Highly stereoselective formation of bicyclic products **193** was observed in both cases, while diastereomers **194** were never detected.

Scheme 55



Further exploration of this approach has met with synthetic challenges and was essentially unrewarded. Numerous experimentations proved that only 1-methyl-2-bromocyclopropane carboxylic acid is fairly suitable for the preparation of starting amides **191**.[115] In situ generation of

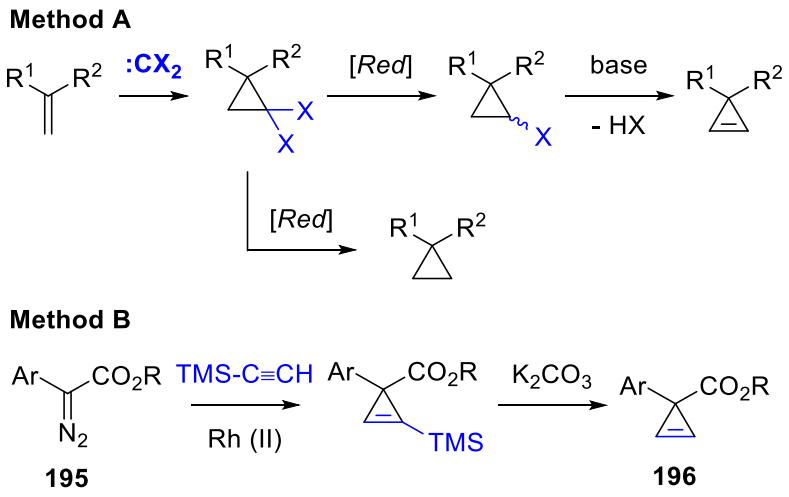
cyclopropenyl amides **192** via 1,2-dehydrohalogenation using analogues of **191** with substituents at the quaternary cyclopropene carbon other than methyl has severe limitations (conditions for the synthesis of other bromocyclopropane starting materials have not been found) rendering this synthetic pathway impractical.

These difficulties warranted further studies to adapt this methodology to more stable, isolable cyclopropenes accessible via the metal-catalyzed cyclopropenation reactions.

4.2 Addition of achiral tethered oxygen-based nucleophiles to cyclopropenes

In order to broaden the scope of base-assisted intermolecular cyclizations of oxygen-based nucleophiles to cyclopropenes we focused on an alternative route to cyclopropenyl amide starting materials **196**, via the Rh(II)-catalyzed [2+1]-cycloaddition of diazoacetates **195** with trimethylsilylacetylene,[134] which was improved and tailored to our systems (Method B in Scheme 56).[135]

Scheme 56

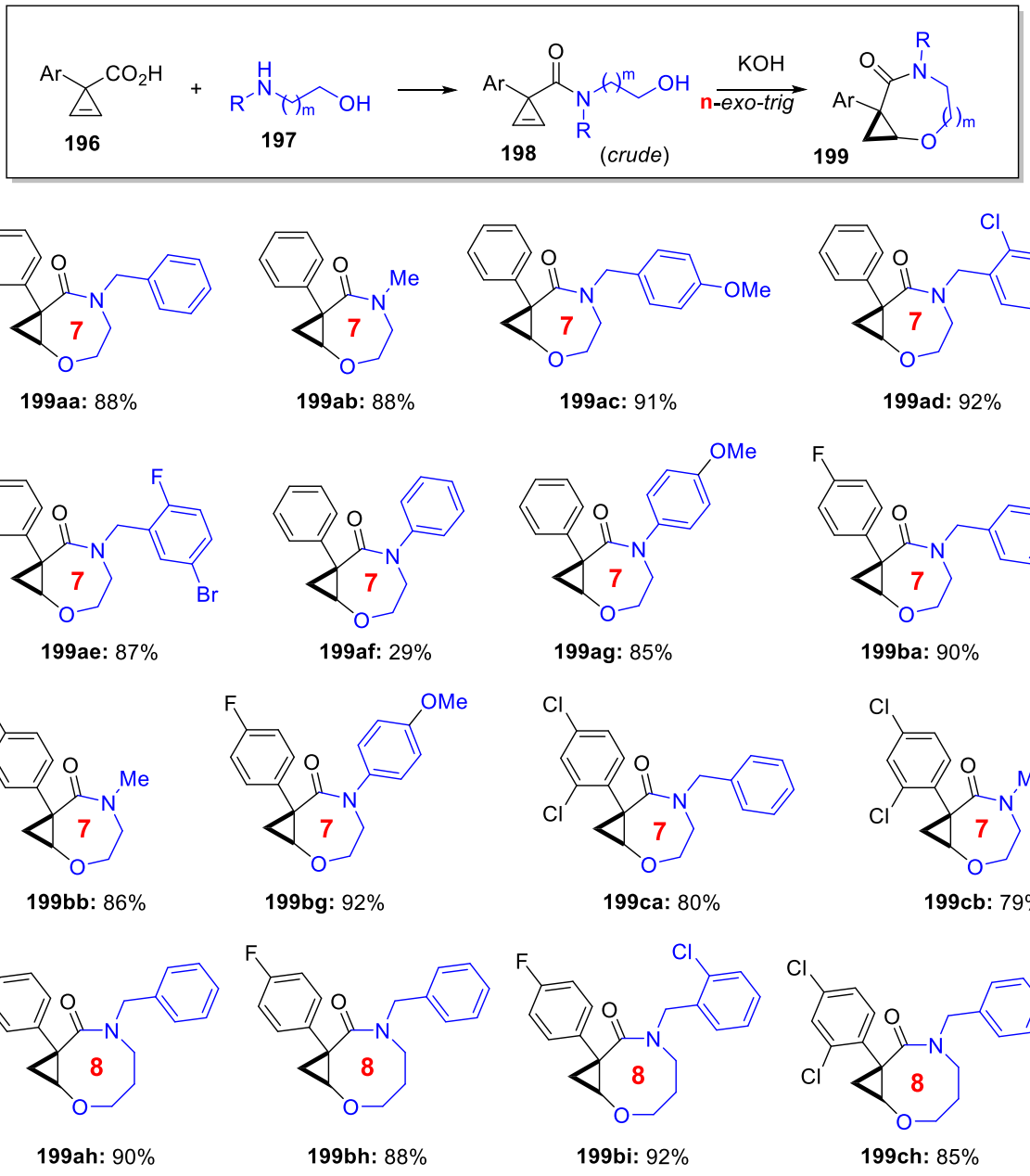


The efficiency of this approach was initially tested using racemic cyclopropene amides **198** derived from achiral amino alcohols **197**. Thus, readily available 1-arylcycloprop-2-ene-1-carboxylic acids **196**[134,135] were derivatized with *N*-protected 2-aminoethanols (**197**, m = 1) and 3-aminopropanols (**197**, m = 2) to afford the corresponding amides **198**, which were used crude in the subsequent base-assisted cyclization (Scheme 57). We first probed the cyclization of amide **198aa**, which reacted smoothly affording oxazabicyclo[5.1.0]octanone **199aa** as a sole product in good yield (Scheme 57).

With the positive initial results in hand, we moved on to evaluate the effect of substituents at nitrogen (R) and sp^3 - hybridized carbon of cyclopropene (Ar) on the cyclization propensity of cyclopropenyl amides **198**. We were pleased to see that *N*-methyl (**199ab**, **199bb**, **199cb**) and various *N*-benzyl 2-oxa-5-azabicyclo[5.1.0]octan-6-ones (**199ac**, **199ad**, **199af**, **199ba**, **199ca**) were efficiently obtained via this approach (Scheme 57). *N*-Phenyl derivative **199af** was produced only in poor yield, which was attributed to a facile base-assisted hydrolysis of the C–N bond in anilides, as noted previously.[115] This side reaction is suppressed in electron-rich anilides, so cyclization of *p*-anisidine derivatives proceeded smoother, affording better yields of oxazepanones **199ag** and **199bg** (Scheme 57). Tethered 3-aminopropanols underwent 8-*exo*-*trig* cyclization efficiently under the same reaction conditions to give oxazocanones **199ah**, **199bh**, **199bi**, and **199ch** (Scheme 57).

Having mapped the substrate scope, we next investigated the possibility of a diastereoselective nucleophilic 7-*exo*-*trig* cyclization of tethered chiral alkoxides with prochiral cyclopropenes.

Scheme 57

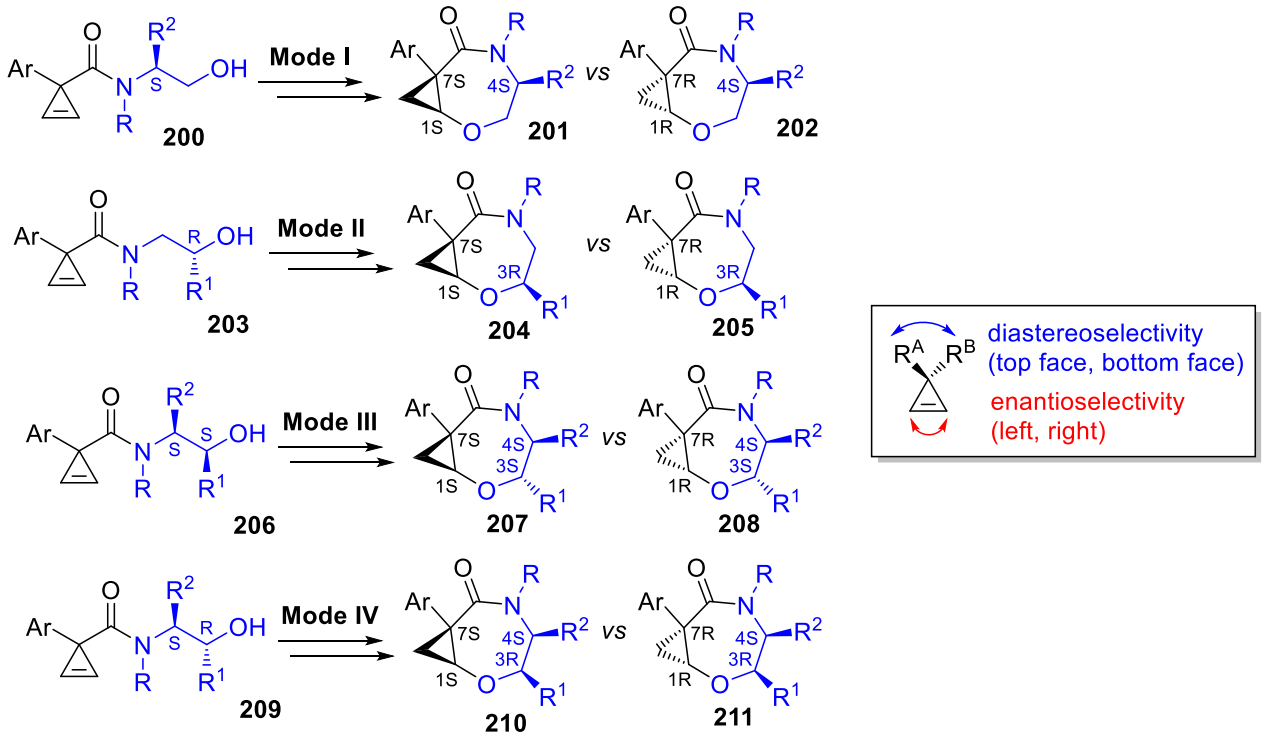


4.3 Stereoselective addition of tethered oxygen-based nucleophiles to cyclopropenes

The two-carbon-atom tether allows for independent installation of two stereogenic centers, which gives rise to four different modes depicted in Scheme 58. Thus, derivatives of chiral aminoethanols with (*S*)-configuration at C-2 (**200**) can potentially produce two products:

(1S,4S,7S)-**201** or (1*R*,4*S*,7*R*)-**202** (mode I in Scheme 58). Likewise, (*R*)-configuration at C-1 in the amino alcohol tether of **203** would give rise to diastereomers (1*S*,3*R*,7*S*)-**204** or (1*R*,3*R*,7*R*)-**205**, respectively (mode II in Scheme 58). Two additional modes are possible when the diastereoselectivity is induced in the presence of two contiguous chiral centers at C-1 and C-2 of the amino alcohol tether. Thus, *threo*-(**206**) could potentially afford products (1*S*,3*S*,4*S*,7*S*)-**207** or (1*R*,3*S*,4*S*,7*R*)-**208** (mode III in Scheme 58), while *erythro*-(**209**) could provide (1*S*,3*R*,4*S*,7*S*)- **210** and (1*R*,3*R*,4*S*,7*R*)-**211**, respectively (mode IV in Scheme 58). The following discussion addresses all the above-mentioned cyclization modes in detail.

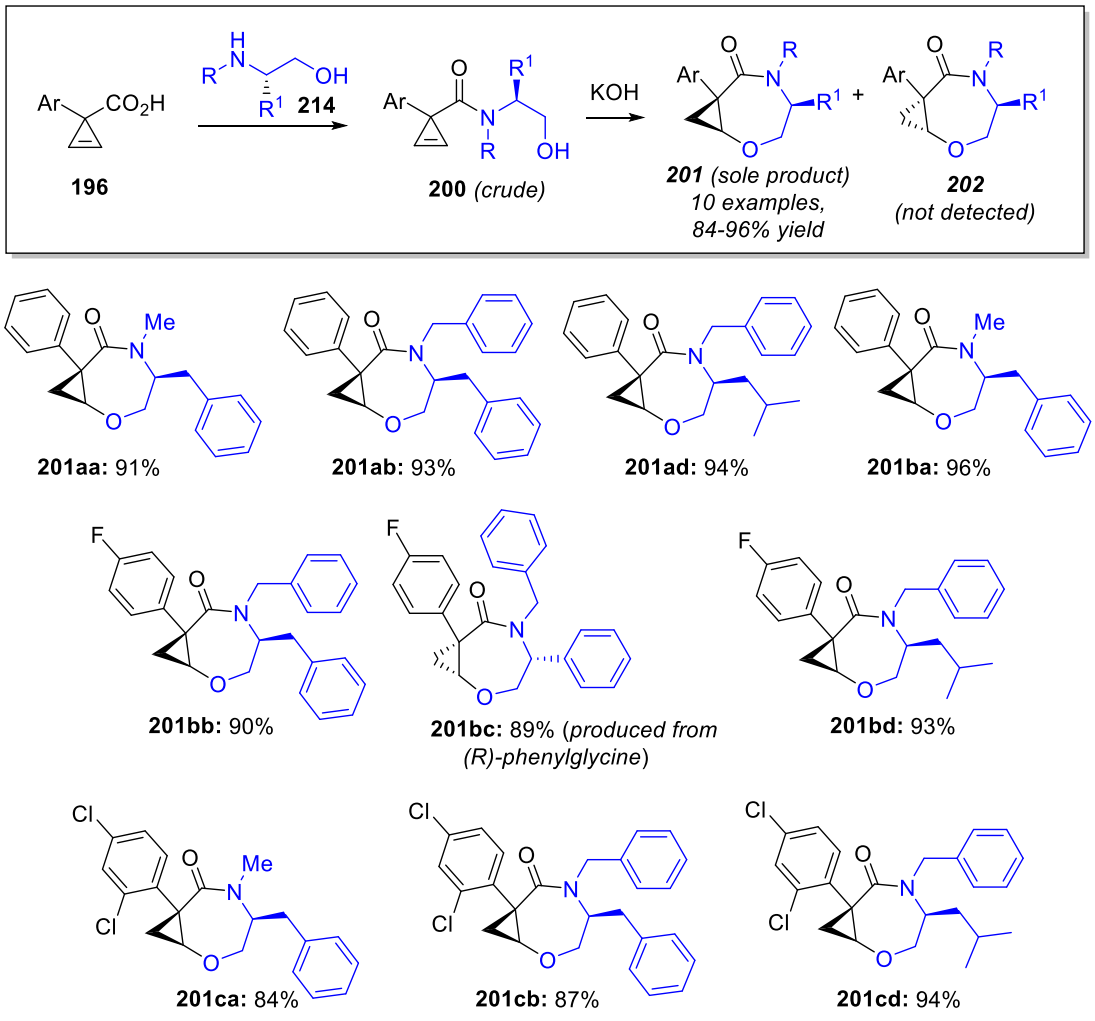
Scheme 58



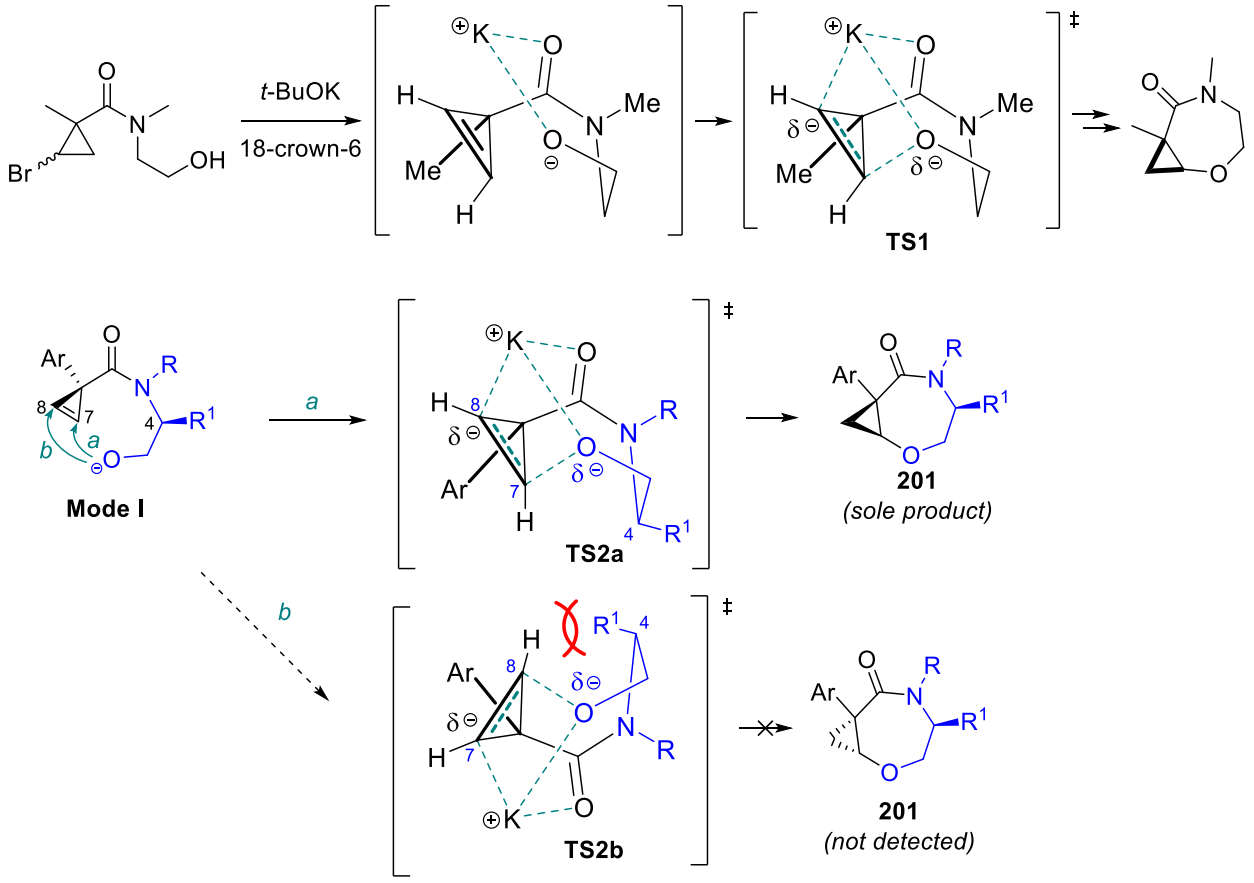
To probe mode I, a set of condensation reactions between 1-arylcycloprop-2-ene-1-carboxylic acids (**196a−c**) and chiral amino alcohols **214b−d** were carried out, and thus obtained chiral

cyclopropenes **200** were used crude in the cyclization (Scheme 59) under the standard reaction conditions described above (Scheme 57). We were very pleased to find that, in all cases, the enantiomerically pure (1*S*,4*S*,7*S*)-2-oxa-5-azabicyclo[5.1.0]octan-6-ones **201** were obtained as sole products (1*R*,4*R*,7*R* enantiomer was obtained for **201bc**, originated from (*R*)-phenylglycinol). None of these reactions produced any detectable amounts of the diastereomers **202**. The relative and absolute configuration of compound **201bd** was unambiguously confirmed by single-crystal X-ray crystallography (CCDC #1823183).[3]

Scheme 59



Scheme 60

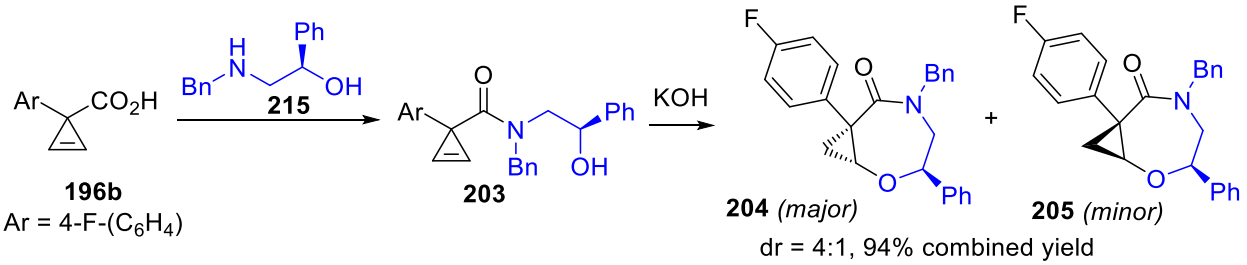


Our rationale for the origins of the high diastereoselectivity obtained in cyclization mode I is shown in Scheme 60. Computational studies performed on achiral models suggested that the transition state in 7-*exo-trig* cyclization (**TS1**) has a very rigid pseudoboat conformation, stabilized by a three-center coordinated potassium cation bound through the alkoxide and carbonyl oxygens as well as the anionic carbon atom.[123b] Assuming the same transition state model is realized for the chiral substrates in the present studies, a nucleophilic attack at the now diastereotopic C-7 or C-8 would result in two nonequivalent reaction pathways ***a*** and ***b***, respectively (Scheme 60). Path ***a***, affording product **201**, operates via a lower-energy transition state **TS2a**, in which substituent

R^1 at C-4 assumes the thermodynamically more favored, pseudoequatorial (bowsprit) conformation. The alternative, higher-energy transition state **TS2b**, resulting from nucleophilic attack ***b***, forces the R^1 group into a pseudoaxial (flagpole) position where it experiences a strong syn-pentane interaction with hydrogen at C-8, which disfavors formation of product **202**.

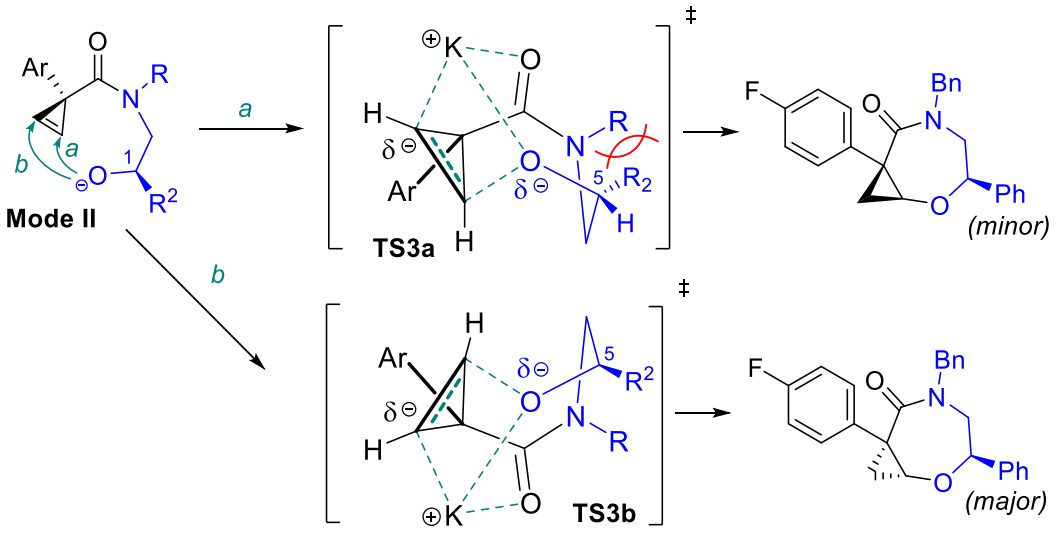
To test mode II, (*R*)-2-(benzylamino)-1-phenylethan-1-ol (**215**) was condensed with cyclopropenyl carboxylic acid **196b**, and the resulting amide **203b** was subjected to the base-assisted cyclization. A 1:4 ratio of two isomeric products, **204b** and **205b**, was obtained (Scheme 61). Configurations of both products were unambiguously assigned by 2D NOESY experiments.[3]

Scheme 61



A mechanistic scenario consistent with the observed marginal diastereoselectivity is outlined in Scheme 62. It is believed that the unfavorable 1,3-diaxial interaction between substituent R^2 at C-5 and the R group at nitrogen in the seven-membered complex **TS3a** (resulting from path ***a***) is not as prohibitive as in cyclohexyl analogues. As a result, **204** is produced as a minor product. An alternative, major pathway ***b*** proceeding via transition state **TS3b**, in which substituent R^2 at the stereogenic center is free of the unfavorable interactions, gives rise to major product **205**.

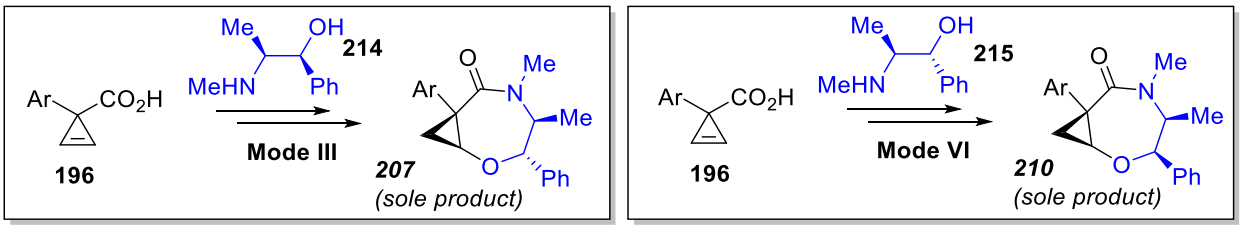
Scheme 62



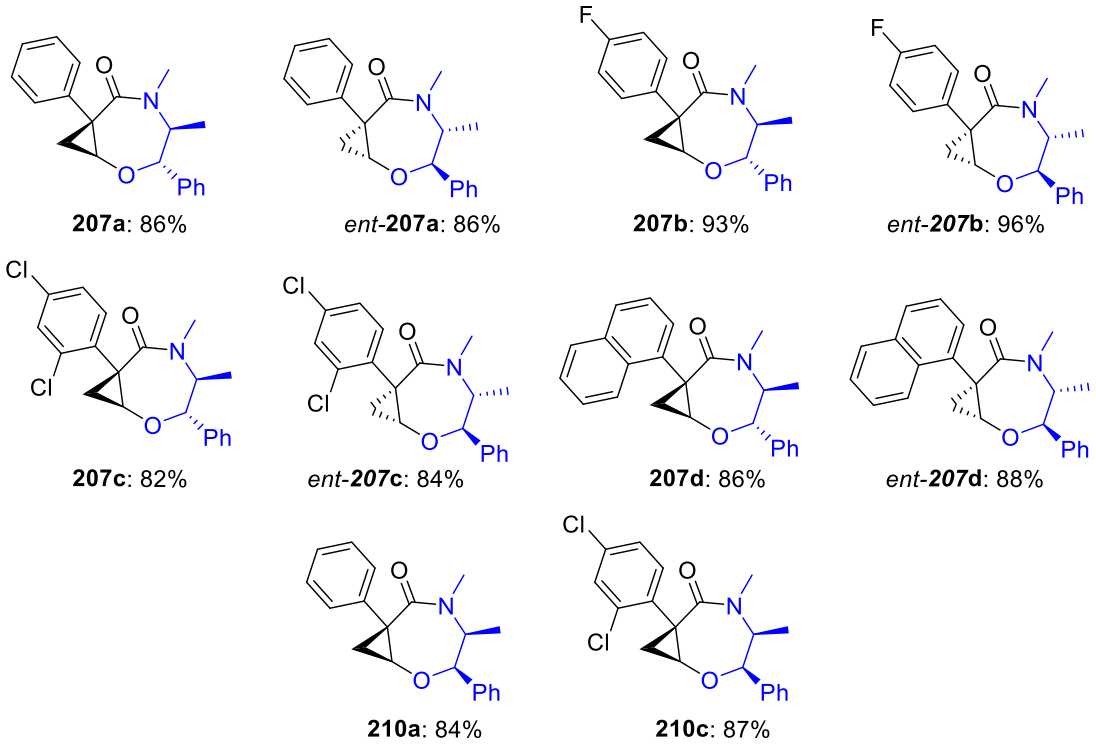
Next, we tested modes III and IV on cyclopropenyl carboxamide derivatives prepared from cyclopropene carboxylic acids **196a−d** and (+)- or (−)-pseudoephedrine (**214** or ent-**214**) and (−)-ephedrine (**215**). Cyclization of these substrates provided oxazepanones **207** (or ent-**207**) and **210**, respectively, as sole products in excellent yields (Scheme 63).

Single-crystal X-ray diffraction analysis unambiguously confirmed the absolute configurations of products **207c** (CCDC # 1823195) and **210c** (CCDC # 1823181).[3]

Scheme 63

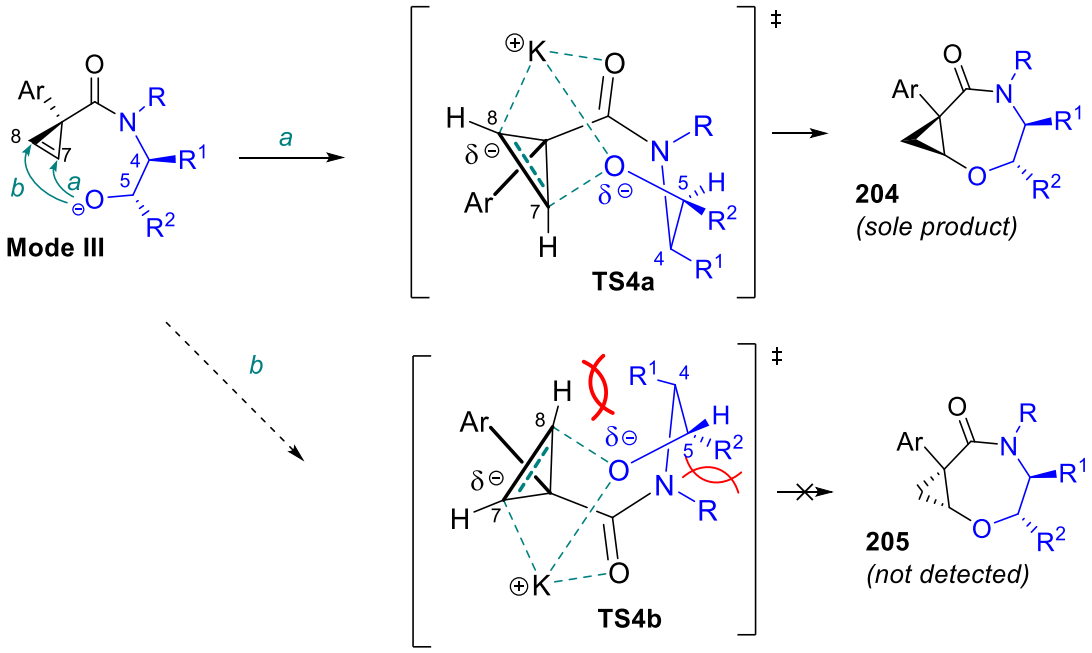


Scheme 63 (continued)



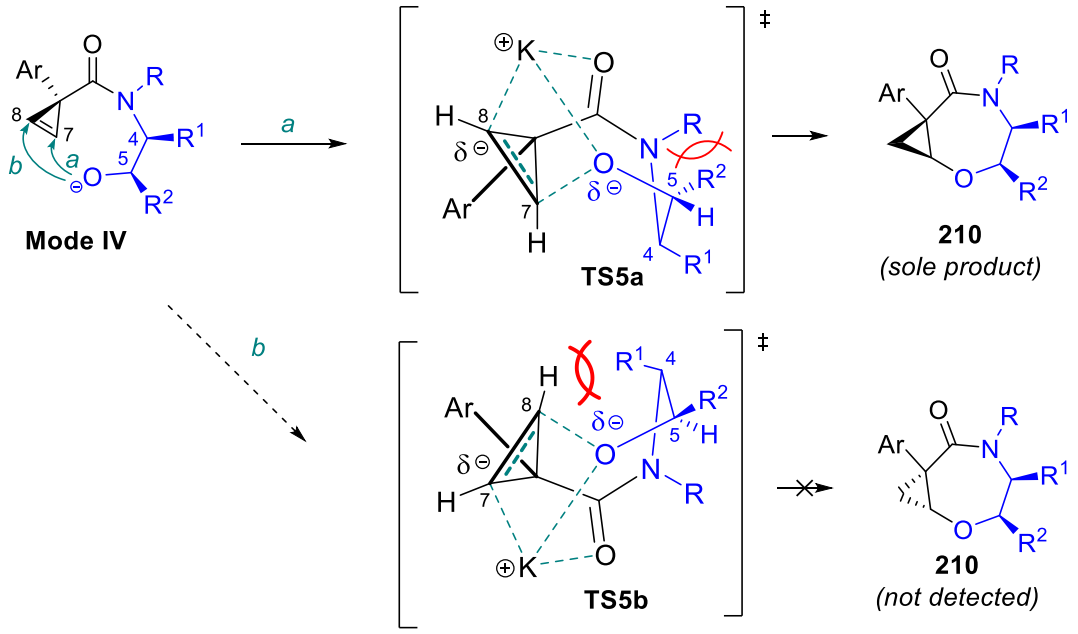
The origins of high diastereoselectivity in the 7-*exo*-*trig* nucleophilic cyclization producing **207** (mode III) are analyzed in Scheme 64. It is believed that the nucleophilic attack at C-7 (path ***a***) is highly preferred due to a more favored transition state **TS4a**, in which both substituents R^1 and R^2 occupy a pseudoequatorial position. A complementary path ***b*** would lead to a much more energetic transition state **TS4b**, in which substituent R^1 in a flagpole orientation is experiencing steric repulsions with hydrogen at C-8, similar to that described above for mode I (Scheme 60). The 1,3-diaxial interaction between substituents R and R^2 could be another contributing factor to destabilization of **TS4b**. This effect, however, is not expected to be significant for small *N*-substituents, such as a methyl group.

Scheme 64



Finally, the high selectivity observed in cyclization mode IV is rationalized as follows (Scheme 65). Transition state **TS5a** resulting from the nucleophilic attack at C-7 (path ***a***) is rather favorable, since the 1,3-diaxial interaction between substituents R and R^2, as was stated above, is quite insignificant for nonbulky R groups. The alternative transition state **TS5b**, resulting from an attack at C-8 (path ***b***), experiences prohibitive steric interactions with a flagpole substituent R^1. Arguably, in all four cyclization modes analyzed above, the stereoselectivity is greatly influenced by configuration of the stereogenic center at C-4 and the R^1 group, while the C-5 substituent R^2 plays a modest role, at least for derivatives with a nonencumbered substituent on the nitrogen. The strong cation-templating effect elicits conformational rigidity of the transition state and amplifies the asymmetric induction arising from a rather remote chiral center, which ultimately allows for the efficient desymmetrization of the cyclopropenyl moiety.

Scheme 65

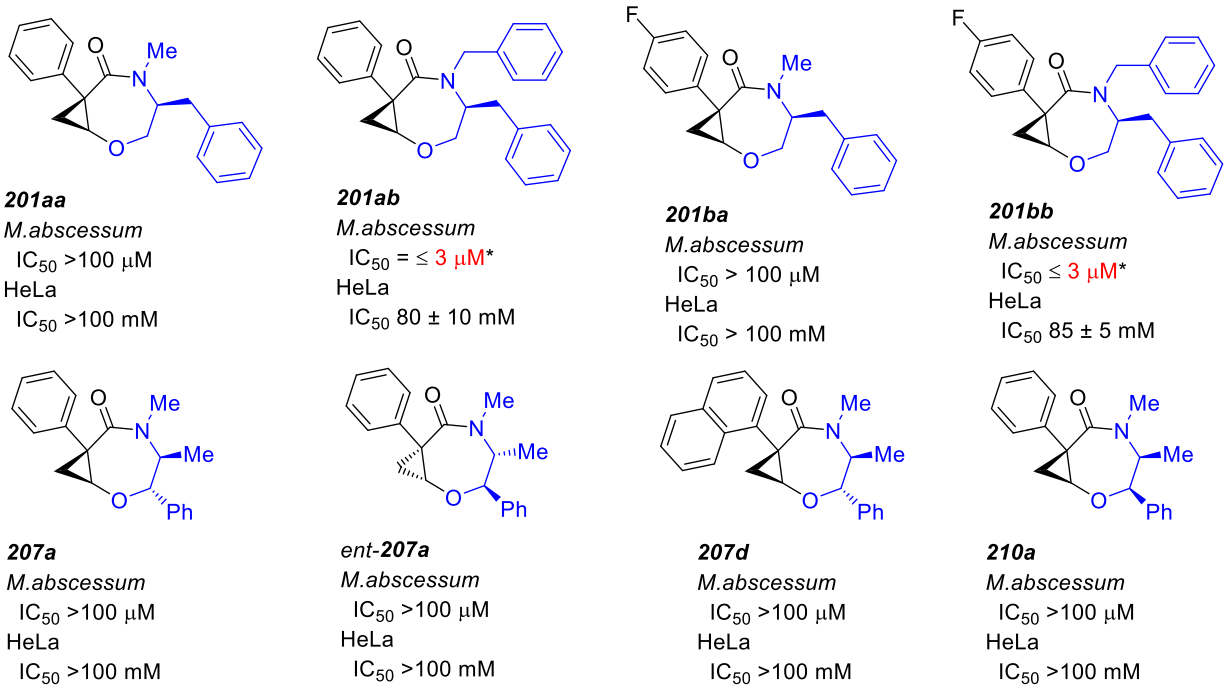


4.5 Biological evaluation of antimicrobial and anticancer activities of azabicyclo[5.1.0]octanones

It should be pointed out that fused oxazepanes are a very important class of biologically active molecules that display diverse pharmacological activities (see Chapter1.3). This class of compounds is known for its antibiotic, anticancer, and antipsychotic bioactivities.[6] Development of new approaches to these important molecules, especially stereoselective, can lead to the discovery of new privilege medicinal structures.

In the preliminary biological studies performed in the collaborative project with the group of Prof. Frolova (New Mexico Institute of Mining and Technology, Socorro, New Mexico), enantiopure 2-oxa-5-azabicyclo[5.1.0]octan-6-ones were shown to be very attractive biological probes.[3] This unique heterocyclic scaffold just recently emerged on the chemical space map and it revealed promising antimicrobial activity against *mycobacterium abscessus*,[136] a rapid growing highly virulent chemotherapy-resistant mycobacterial pathogen.

Preliminary biological evaluation of a few representative compounds for antimicrobial and anticancer activities was performed by the group of Prof. Frolova. The antiproliferative activity was assessed by using the cancer cell line, HeLa, as a model for human cervical adenocarcinoma, through the measurements of mitochondrial dehydrogenase activities using the MTT method.[137] In addition, the synthesized compounds were tested against *staphylococus epidermidis* and *escherichia coli*, where minimum inhibitory concentrations (MICs) were determined by the broth microdilution method using MTT assay.[138] Since the described compounds bear some similarity with azepanes known to possess activity against mycobacteria,[139] products **201**, **207**, and **210** were also tested against *mycobacterium abscessus* by MTT assay. The potency of synthesized compounds against yeasts was also evaluated using *candida albicans*.



** >50% reduction in viability was observed at 3.13 μM treatment for compounds **201ab** and **201bb**, but the absence of data at lower concentrations prevented determination of an accurate IC_{50} value. See A1 section of Appendix for more details. Additionally, further reductions in viability were not observed upon treatment with higher concentrations of these compounds*

Figure 14. Biological activity of selected 2-oxa-5-azabicyclo[5.1.0]octan-6-ones

This preliminary tests revealed that none of these compounds demonstrated any activity against *candida albicans*, *staphylococus epidermidis*, or *escherichia coli* up to 100 μM nor significant cytotoxicity on HeLa cells. However, promising activity against *mycobacterium abscessus* was observed for selected 2-oxa-5-azabicyclo[5.1.0]octan-6-ones (Figure 14). The latter finding, coupled with apparent low general toxicity against cultured human cells, set the grounds for further SAR studies.

See section A1 of Appendix for experimental data.

4.6 Conclusion

The development of a synthetic approach that allows for modular assembly of enantiopure cyclopropane-fused oxazepanones is reported. A strain-release-driven, cation-templated intramolecular nucleophilic addition of tethered alkoxides to prochiral cyclopropenes has been developed. The scope of this cyclization and the mechanism of enantiomeric induction were investigated on a series of tethered chiral alkoxides. Three out of four tested chiral cyclization modes provided a highly efficient asymmetric induction. It was shown that the chiral center at C-4 plays a crucial role in controlling desymmetrization of the cyclopropenyl moiety, instigated by a profound potassium-templated effect.

The obtained optically active 2-oxa-5-azabicyclo[5.1.0]octan-6-ones were tested against representative mycobacterial infection-causing organisms as well as other bacteria, pathogenic fungi, and human cancer cell lines. The biological profile exhibited by some of these unique chiral cyclopropane-fused medium-sized heterocycles is characterized by promising activity against *mycobacterium abscessus* coupled with apparent low general toxicity against cultured human cells.

4.7 Experimental

4.7.1 General information

NMR spectra were recorded on a Bruker Avance DRX- 500 (500 MHz) with a dual carbon/proton cryoprobe (CPDUL), Bruker III (400 MHz) equipped with BBO probe. ^{13}C NMR spectra were registered with broadband decoupling. The (+) and (−) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. IR spectra were recorded on a ThermoFisher Nicolet iS 5 FT-IR spectrometer. HRMS was carried out on an LCT Premier (Micromass Technologies) instrument employing ESI TOF detection techniques. Glassware used in moisture-free syntheses was flame-dried in a vacuum prior to use. Column chromatography was carried out on silica gel (Sorbent Technologies, 40 − 63 mm). Silica gel plates (Sorbent Technologies Silica XG 200 mm) were used for TLC analyses. Anhydrous dichloromethane was obtained by passing degassed commercially available HPLC-grade inhibitor-free solvent consecutively through two columns filled with activated alumina and stored over molecular sieves under nitrogen. Water was purified by dual-stage deionization followed by dual-stage reverse osmosis. Anhydrous THF was obtained by refluxing commercially available solvent over calcium hydride followed by distillation in a stream of dry nitrogen. 1-Phenylcycloprop-2-ene-1-carboxylic acid (**196a**), [140] 1-(4-fluorophenyl)-cycloprop-2-ene-1-carboxylic acid (**196b**),[117k] and (S)-2-(benzylamino)-4-methylpentan-1-ol (**214d**) [141] were synthesized according to the previously published procedures and had physical and spectral properties identical to those earlier reported. Syntheses of 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**), 1-(naphthalen-1-yl)cycloprop-2-ene-1-carboxylic acid (**196d**), and 2-((5-bromo-2-fluorobenzyl)amino)ethan-1-ol (**197e**) are described in Chapter 4.7.3. All other reagents and solvents were purchased from commercial vendors and used as received.

4.7.2 Biological Studies: Materials and Methods

All culture cell lines were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA).

Cell Culture. HeLa cells were cultured in DMEM supplemented with 10% fetal bovine serum (FBS). To evaluate antiproliferative properties of the synthesized compounds, the cells were trypsinized and seeded at $4 \cdot 10^3$ cells per well into 96-well microtiter plates. The cells were grown for 24 h before treatment.

Fungal Culture. *Candida albicans* (ATCC 26555) was grown overnight in Difco YM Broth at 37 °C in a shaking incubator.

Bacterial Cultures. *Mycobacterium abscessus* (ATCC 19977) was inoculated in Middlebrook 7H9 medium supplemented with 1% ADC enrichment and incubated at 37 °C in T25 tissue culture flasks for 72 h.

Staphylococus epidermidis and *escherichia coli* were incubated in Tryptic Soy Broth (TSB) for 6 h at 37 °C.

MTT assay for HeLa (ATCC CCL-2). All compounds were dissolved in DMSO at a concentration of either 100 or 50 mM prior to cell treatment. The cells were treated at concentrations ranging from 0.004 to 100 μM and incubated for 48 h in 200 μL of media. An amount of 20 μL of MTT reagent in serum-free medium (5 mg/mL) was added to each well and incubated further for 2 h. Media was removed, and the resulting formazan crystals were solubilized in 100 μL of DMSO. A490 was measured using a Thermomax Molecular Device plate reader. The experiments were performed in quadruplicate and repeated at least twice for each compound per cell line. Cells treated with 0.1% DMSO were used as a vehicle control, and phenyl arsine oxide (PAO) was used as a positive killing control.

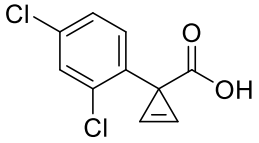
MTT assay for candida albicans (ATCC 26555). Cells were diluted 1:20 in YM Broth. 2-Fold serial dilutions were prepared as follows: 1000 μL of cells was added to the first well of each 24-well plate, and 500 μL of cells was added to the proceeding wells. Compounds were added at a final concentration of 100 μM. 2-Fold dilutions were continued across all remaining wells. Cells were incubated for 24 h at 37 °C and then treated with 100 μL of MTT (5 mg/mL) and incubated for 3 h. An equal volume of premixed solution of 50% dimethylformamide with 20% sodium dodecyl sulfate (solubilization solution) was added to dissolve the formazan crystals and incubated further for 15 min. The experiments were performed in triplicate. Amphotericin B was used as positive kill control, and untreated cells served as negative controls.

MTT assay for staphylococus epidermidis (ATCC 35984) and Escherichia coli (ATCC 25922). An overnight cell growth was diluted to an optical density of 0.100 at A595; cells were further diluted 1:100 in TSB. An amount of 1000 μL of the dilution was added to each well of a 12-well plate (except the first well, which received only TSB). Each well received one compound at a final concentration of 100 μM. Plates were incubated for 24 h at 37 °C. Cells were subsequently treated with 100 μL of MTT (5 mg/mL) and incubated at 37 °C for 15 min. Solubilization solution was added to dissolve the formazan crystals and incubated further for 15 min. An amount of 50 μg/mL of colistin (PME) was used as a positive kill control for E. coli; 50 μg/mL of vancomycin was used as a positive kill control for S. epidermidis; and untreated cells served as negative controls. The experiments were performed in triplicate.

MTT assay for mycobacterium abscessus (ATCC 19977). Approximately $5.5 \cdot 10^5$ mycobacteria per mL or a dilution of 1:500 from an overnight growth were plated at a final volume of 400 μL/well in 48-well plates. Compounds were initially screened at a concentration of 100 μM on *M. abscessus*. Compounds with antimycobacterial activity at 100 μM were screened for further

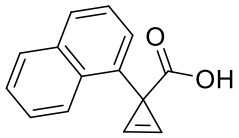
activity by adding the selected compounds to cells at a concentration of 50 μM and 2-fold serially diluting. The plates were incubated in a shaking incubator for 48 h at 37 °C. Following the incubation, 40 μL or 10% w/v of MTT reagent (5 mg/mL) was added to each of the wells. The plates were incubated for 2 h at 37 °C. An amount of 650 μL of solubilization solution was added to each of the wells, and the plate was incubated at 37 °C for an additional 12 h. An amount of 100 μL from each well was transferred into a clear 96-well microtiter plate, and A595 was read in a Thermomax Molecular Device plate reader. Wells containing Middlebrook 7H9 medium and nontreated cells served as negative controls, and a well containing 10 μM PAO-treated cells served as a positive kill control. The experiments were performed in triplicate.

4.7.3 Synthesis of Starting Materials

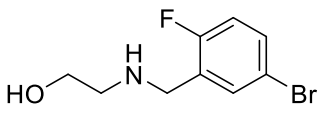


1-(2,4-Dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**) Solution methyl 1-(2,4-dichlorophenyl)-2-(trimethylsilyl)cycloprop-2-ene-1-carboxylate (3.71 g, 11.77 mmol, 1.00 equiv.) in a 1 : 1 mixture of methanol : THF (100 mL) was stirred at 0 °C. A 1.5 M aqueous solution of NaOH (102 mL, 153.0 mmol, 13.0 equiv.) was added dropwise and the mixture was stirred for 18 h. Organic solvents were then removed under vacuum and the remaining aqueous solution was washed with dichloromethane (3 × 50 mL). The remaining aqueous phase was acidified to pH 2 with 1 N aqueous HCl and extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.27, mp 194-195 ^oC). Yield 2.10 g (9.16 mmol, 78 %). ^1H NMR (400 MHz, $CDCl_3$) δ 11.88 (s, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.28 (s, 2H), 7.19 (dd, J = 8.2, 2.1 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H). ^{13}C

NMR (126 MHz, $CDCl_3$) δ 180.9, 137.9, 135.9, 133.9, 131.2 (+), 129.4 (+), 127.5 (+), 108.0 (+, 2C), 29.4. FTIR (NaCl, cm^{-1}): 3155, 3115, 2975, 2835, 1697, 1661, 1472, 1302, 1267, 1113, 985, 934, 805, 630. HRMS (TOF ES): found 226.9671, calculated for $C_{10}H_5Cl_2O_2$ (M–H) 226.9667 (1.8 ppm).



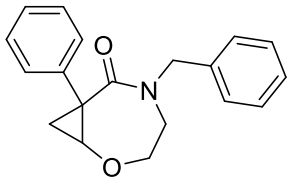
1-(Naphthalen-1-yl)cycloprop-2-ene-1-carboxylic acid (**196d**) Solution of methyl 1-(naphthalen-1-yl)-2-(trimethylsilyl)cycloprop-2-ene-1-carboxylate (3.82 g, 12.9 mmol, 1.00 equiv.) in a 1 : 1 mixture of methanol : THF (100 mL) was stirred at 0 °C. A 1.5 M aqueous solution of NaOH (112 mL, 167.7 mmol, 13.0 equiv.) was added dropwise and the mixture was stirred for 18 h. Organic solvents were then removed under vacuum and the remaining aqueous phase was washed with dichloromethane (3 × 50 mL). The remaining aqueous solution was acidified to pH 2 with 1 N aqueous HCl and extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.27, mp 144-145 °C). Yield 2.23 g (10.6 mmol, 82 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.42 (br. s, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.55–7.46 (m, 2H), 7.45 (s, 2H), 7.41 (t, J = 7.7 Hz, 1H), 7.34 (d, J = 6.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.9, 138.1, 133.9, 132.0, 128.9 (+), 128.2 (+), 126.3 (+), 126.0 (+), 125.9 (+), 125.8 (+), 124.3 (+), 108.8 (+, 2C), 29.1. FTIR (NaCl, cm^{-1}): 3162, 3122, 3048, 2975, 1691, 1656, 1410, 1264, 1237, 1120, 990, 775, 733, 640. HRMS (TOF ES): found 209.0593, calculated for $C_{14}H_9O_2$ (M–H) 209.0603 (4.8 ppm).



2-((5-bromo-2-fluorobenzyl)amino)ethan-1-ol (**197e**). 5-Bromo-2-fluorobenzaldehyde (2 mL, 3.42 g, 16.8 mmol, 1.0 equiv.), 2-

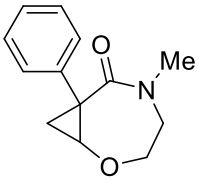
aminoethan-1-ol (1.12 mL, 1.13 g, 18.5 mmol, 1.1 equiv.), and 30 mL of anhydrous methanol were combined and stirred at RT overnight. Reaction mixture was cooled to 0 °C, $NaBH_4$ (955 mg, 25.3 mmol, 1.5 equiv.) was added in portions, and reaction mixture was stirred for 2 hours at RT. Reaction mixture was concentrated in vacuum and partitioned between 10 mL of water and 10 mL of dichloromethane. The aqueous phase was then extracted with dichloromethane (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated to yield the title compound as a colorless solid (mp 75-76 °C). Yield 3.34 g (13.5 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 6.6, 2.5 Hz, 1H), 7.38–7.31 (m, 1H), 6.98–6.88 (m, 1H), 3.83 (s, 3H), 3.70–3.64 (m, 2H), 2.83–2.76 (m, 2H), 1.95 (br. s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3 (d, *J* = 246.1 Hz), 133.1 (d, *J* = 5.0 Hz, +), 131.7 (d, *J* = 8.2 Hz, +), 129.5 (d, *J* = 16.4 Hz), 117.3 (d, *J* = 23.6 Hz, +), 116.8 (d, *J* = 3.6 Hz), 61.1 (–), 50.4 (–), 46.6 (d, *J* = 2.7 Hz, –). FTIR (NaCl, cm^{-1}): 33020 (br), 2924, 2843, 1483, 1236, 1171, 1069, 814, 621; HRMS (TOF ES): found 248.0092, calculated for $C_9H_{12}BrFNO$ (M + H) 248.0086 (2.4 ppm).

4.7.4 Cyclization of Achiral Substrates

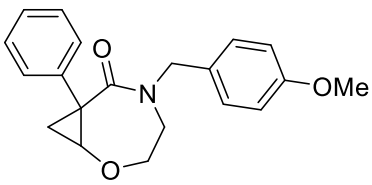


5-Benzyl-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199aa**). *Typical Procedure*: Flame-dried round bottom flask was charged with 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (500 mg, 3.12 mmol, 1.0 equiv.), DMF (2 drops) and freshly distilled anhydrous dichloromethane (7 mL) under nitrogen atmosphere. Oxalyl chloride (400 μL, 592 mg, 4.68 mmol, 1.5 equiv.) was then added dropwise and the mixture was stirred at room temperature for 2 h. The solution was concentrated in a stream of nitrogen; the residue was subjected to a high vacuum, dissolved in anhydrous dichloromethane (2.0 mL) and added dropwise to a stirred solution of 2-(benzylamino)ethan-1-ol (**197a**) (708 mg,

4.68 mmol, 1.5 equiv.) and triethylamine (1.3 mL, 948 mg, 9.36 mmol, 3.0 equiv.) in anhydrous dichloromethane (3.0 mL). The reaction mixture was stirred at room temperature for 18 hours and then partitioned between water (15 mL) and dichloromethane (20 mL). The aqueous phase was acidified with 5 mL of 2N HCl. The organic phase was then washed with 2N HCl (3 x 10 mL). The combined aqueous layers were back-extracted once with 10 mL of dichloromethane, which was combined with other organic phases, washed with brine, dried with $MgSO_4$, filtered, and concentrated. The product, *N*-benzyl-*N*-(2-hydroxyethyl)-1-phenylcycloprop-2-ene-1-carboxamide (**198aa**) was filtered through a silica plug using EtOAc, and was used at the cyclization step as is without additional purification. An oven-dried 1 mL Wheaton vial was charged with powdered KOH (7.6 mg, 0.136 mmol, 2.0 equiv) and anhydrous THF (400 μL). Crude amide **198aa** (20 mg, 0.068 mmol) was added as a solution in anhydrous THF (400 μL). The mixture was vigorously stirred at 30 °C for 18 h, then the reaction mixture was filtered through short plug of Silica gel eluting with EtOAc, and the eluate was concentrated in vacuum. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless oil (R_f 0.25). Yield 17.6 mg (0.060 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 7H), 7.25–7.21 (m, 1H), 7.10–7.08 (m, 2H), 4.71 (q, *J* = 14.7 Hz, 2H), 3.92 (ddd, *J* = 15.5, 12.6, 5.1 Hz, 1H), 3.53 (dd, *J* = 11.2, 5.1 Hz, 1H), 3.43 (dd, *J* = 6.3, 3.7 Hz, 1H), 3.41–3.36 (m, 1H), 3.03 (dt, *J* = 23.2, 11.6 Hz, 1H), 1.75 (dt, *J* = 24.0, 12.0 Hz, 1H), 1.49 (dd, *J* = 6.9, 6.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 138.0, 137.3, 128.9 (+, 2C), 128.8 (+, 2C), 128.4 (+, 2C), 127.8 (+), 126.8 (+), 124.7 (+, 2C), 64.4 (–), 59.0 (+), 49.8 (–), 44.9 (–), 34.9, 22.5 (–). FTIR (NaCl, cm^{-1}): 3026, 2967, 1651, 1497, 1408, 1209, 1057, 1028, 748, 696; HRMS (TOF ES): found 294.1501, calculated for $C_{19}H_{20}NO_2$ (M + H) 294.1494 (2.4 ppm).

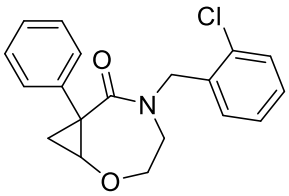


5-Methyl-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199ab**). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and 2-(methylamino)ethan-1-ol (**197b**) (141 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-(2-hydroxyethyl)-*N*-methyl-1-phenylcycloprop-2-ene-1-carboxamide (**198ab**) was used at the cyclization step as is without additional purification To this end, amide **198ab** (20 mg, 0.092 mmol) was treated with powdered KOH (10.3 mg, 0.184 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless glass (R_f 0.21). Yield 17.6 mg (0.081 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.27 (m, 2H), 7.25–7.19 (m, 1H), 7.05 (d, *J* = 7.9 Hz, 2H), 4.06 (ddd, *J* = 15.4, 12.7, 5.0 Hz, 1H), 3.82 (td, *J* = 11.9, 4.6 Hz, 1H), 3.64 (dd, *J* = 11.2, 5.0 Hz, 1H), 3.40 (dd, *J* = 6.2, 3.6 Hz, 1H), 3.08 (s, 3H), 3.03 (dd, *J* = 15.4, 4.7 Hz, 1H), 1.66 (dd, *J* = 6.9, 3.5 Hz, 1H), 1.45 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 137.9, 128.9 (+, 2C), 126.8 (+), 124.7 (+, 2C), 63.3 (–), 58.8 (+), 47.6 (–), 34.9, 34.3 (+), 22.3 (–). FTIR (NaCl, cm^{-1}): 2961, 1651, 1495, 1431, 1395, 1260, 1169, 1061, 1030, 797, 752, 696. HRMS (TOF ES): found 240.1003, calculated for $C_{13}H_{15}NO_2Na$ (M + Na) 240.1000 (1.2 ppm).



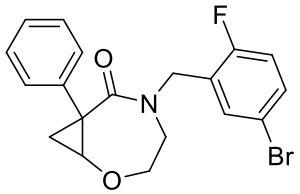
5-(4-Methoxybenzyl)-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199ac**). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and 2-((4-methoxybenzyl)amino)ethan-1-ol (**197c**) (339 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-(2-

hydroxyethyl)-*N*-(4-methoxybenzyl)-1-phenylcycloprop-2-ene-1-carboxamide (**198ac**) was used at the cyclization step as is without additional purification. To this end, amide **198ac** (20 mg, 0.062 mmol) was treated with powdered KOH (6.9 mg, 0.124 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.21, mp 102-104 °C). Yield 18.2 mg (0.056 mmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2H), 7.26–7.20 (m, 3H), 7.09–7.06 (m, 2H), 6.88–6.84 (m, 2H), 4.73 (d, *J* = 14.5 Hz, 1H), 4.57 (t, *J* = 11.7 Hz, 1H), 3.92–3.84 (m, 1H), 3.80 (s, *J* = 2.5 Hz, 3H), 3.51 (dd, *J* = 11.1, 5.1 Hz, 1H), 3.40 (dt, *J* = 11.1, 5.6 Hz, 1H), 3.34 (ddd, *J* = 12.5, 11.2, 4.9 Hz, 1H), 3.03 (dd, *J* = 15.4, 4.8 Hz, 1H), 1.74 (dd, *J* = 7.0, 3.6 Hz, 1H), 1.52–1.45 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 159.3, 138.0, 129.7 (+, 2C), 129.4 (+), 128.9 (+, 2C), 126.7 (+), 124.7 (+, 2C), 114.2 (+, 2C), 64.5 (–), 59.0 (+), 55.4 (+), 49.2 (–), 44.7 (–), 35.0, 22.5 (–); FTIR (NaCl, cm^{-1}): 2957, 2866, 1647, 1512, 1464, 1437, 1416, 1248, 1177, 1061, 1032, 806, 752, 698. HRMS (TOF ES): found 346.1412, calculated for $C_{20}H_{21}NO_3Na$ (M + Na) 346.1419 (2.0 ppm).



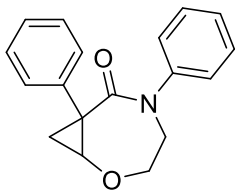
5-(2-Chlorobenzyl)-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199ad**). This compound was synthesized according to the Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and 2-((2-chlorobenzyl)amino)ethan-1-ol (**197d**) (348 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-(2-chlorobenzyl)-*N*-(2-hydroxyethyl)-1-phenylcycloprop-2-ene-1-carboxamide (**198ad**) was isolated and used at the cyclization step without additional purification. To this end, amide **198ad** (20 mg, 0.061 mmol) was treated with powdered KOH (6.8 mg, 0.122 mmol). The titled product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless oil (R_f 0.31). Yield

18.4 mg (0.056 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.37 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.28–7.18 (m, 3H), 7.14–7.07 (m, 2H), 4.94 (d, *J* = 15.4 Hz, 1H), 4.77 (d, *J* = 15.4 Hz, 1H), 3.99 (ddd, *J* = 15.5, 12.3, 5.4 Hz, 1H), 3.63–3.49 (m, 2H), 3.47 (dd, *J* = 6.2, 3.6 Hz, 1H), 3.10 (dd, *J* = 15.4, 4.5 Hz, 1H), 1.75 (dd, *J* = 7.0, 3.6 Hz, 1H), 1.48 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 137.9, 134.9, 133.6, 130.0 (+), 129.7 (+), 129.0 (+), 129.0 (+, 2C), 127.4, 126.8, 124.8 (+, 2C), 64.4 (–), 58.8 (+), 47.1 (–), 45.4 (–), 34.9, 22.6 (–). FTIR (NaCl, cm^{-1}): 3059, 2970, 2868, 1655, 1464, 1431, 1417, 1202, 1153, 1061, 1031, 752, 696. HRMS (TOF ES): found 328.1112, calculated for $C_{19}H_{19}ClNO_2$ (M + H) 328.1104 (2.4 ppm).

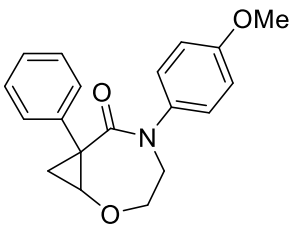


5-(5-Bromo-2-fluorobenzyl)-7-phenyl-2-oxa-5-azabicyclo-[5.1.0]octan-6-one (**199ae**). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (250 mg, 1.56 mmol, 1.0 equiv.), and 2-((5-bromo-2-fluorobenzyl)amino)ethan-1-ol (**197e**) (581 mg, 2.34 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-(5-bromo-2-fluorobenzyl)-*N*-(2-hydroxyethyl)-1-phenylcycloprop-2-ene-1-carboxamide (**198ae**) was isolated and used at the cyclization step without additional purification. To this end, amide **198ae** (20 mg, 0.051 mmol) was treated with powdered KOH (5.7 mg, 0.102 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless oil (R_f 0.31). Yield 17.4 mg (0.045 mmol, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 6.6, 2.5 Hz, 1H), 7.40–7.35 (m, 1H), 7.35–7.29 (m, 2H), 7.26–7.20 (m, 1H), 7.07 (dd, *J* = 5.2, 3.3 Hz, 2H), 6.95 (t, *J* = 9.1 Hz, 1H), 4.87 (d, *J* = 15.2 Hz, 1H), 4.54 (d, *J* = 15.2 Hz, 1H), 4.00 (ddd, *J* = 15.6, 11.4, 6.3 Hz, 1H), 3.66–3.54 (m, 2H), 3.46 (dd, *J* = 6.2, 3.6 Hz, 1H), 3.13–3.03 (m, 1H), 1.74

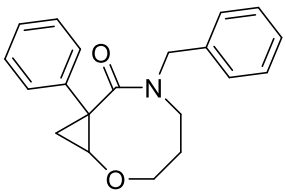
(dd, *J* = 7.0, 3.6 Hz, 1H), 1.48 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 160.1 (d, *J* = 246.4 Hz), 137.7, 133.4 (d, *J* = 4.2 Hz, +), 132.4 (d, *J* = 8.2 Hz, +), 129.0 (+, 2C), 126.9 (+), 126.7 (d, *J* = 16.3 Hz), 124.7 (+, 2C), 117.3 (d, *J* = 23.5 Hz, +), 117.1 (d, *J* = 3.4 Hz), 64.2 (–), 58.8 (+), 45.7 (–),43.2 (d, *J* = 3.7 Hz, –), 34.8, 22.6 (–). FTIR (NaCl, cm^{-1}): 3055, 2922, 2851, 1643, 1591, 1478, 1445, 1252, 1113, 1026, 789, 750, 696. HRMS (TOF ES): found 412.0320, calculated for $C_{19}H_{17}BrFNO_2Na$ (M + Na) 412.0324 (1.0 ppm).



5,7-Diphenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199af**). This compound was synthesized according to the Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and 2-(phenylamino)ethan-1-ol (**197f**) (257 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a Silica gel plug crude *N*-(2-hydroxyethyl)-*N*,1-diphenylcycloprop-2-ene-1-carboxamide (**198af**) was isolated and used at the cyclization step without additional purification. To this end, amide **198af** (20 mg, 0.072 mmol) was treated with powdered KOH (8 mg, 0.144 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless glass (R_f 0.48). Yield 5.8 mg (0.021 mmol, 29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.38–7.31 (m, 4H), 7.30–7.25 (m, 2H), 7.19–7.16 (m, 2H), 4.37 (ddd, *J* = 15.4, 12.6, 4.9 Hz, 1H), 3.94 (ddd, *J* = 12.5, 11.5, 4.8 Hz, 1H), 3.76 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.54 (dd, *J* = 6.3, 3.6 Hz, 1H), 3.47 (dd, *J* = 15.4, 4.7 Hz, 1H), 1.83 (dd, *J* = 7.1, 3.6 Hz, 1H), 1.55 (dd, *J* = 7.0, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 142.3, 137.8, 129.4 (+, 2C), 129.0 (+, 2C), 127.1 (+), 126.9 (+), 126.4 (+, 2C), 124.7 (+, 2C), 64.9 (–), 59.3 (+), 49.1 (–), 35.4, 22.6 (–). FTIR (NaCl, cm^{-1}): 3057, 2961, 2920, 1663, 1493, 1398, 1231, 1215, 1157, 1055, 757, 698. HRMS (TOF ES): found 280.1336, calculated for $C_{18}H_{18}NO_2$ (M + H) 280.1338 (0.7 ppm).

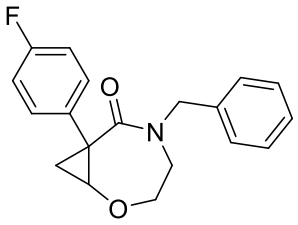


5-(4-Methoxyphenyl)-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199ag**). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and 2-((4-methoxyphenyl)amino)ethan-1-ol (**197g**) (313 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-(2-hydroxyethyl)-*N*-(4-methoxyphenyl)-1-phenylcycloprop-2-ene-1-carboxamide (**198ag**) was used at the cyclization step as is without additional purification. To this end, amide **198ag** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless glass (R_f 0.26). Yield 17 mg (0.055 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.6 Hz, 2H), 7.29–7.20 (m, 3H), 7.16 (d, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.34 (ddd, *J* = 15.4, 12.6, 4.9 Hz, 1H), 3.92 (td, *J* = 12.0, 4.7 Hz, 1H), 3.81 (s, 3H), 3.73 (dd, *J* = 11.3, 4.9 Hz, 1H), 3.52 (dd, *J* = 6.2, 3.6 Hz, 1H), 3.38 (dd, *J* = 15.3, 4.7 Hz, 1H), 1.81 (dt, *J* = 20.0, 10.0 Hz, 1H), 1.53 (t, *J* = 6.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 158.4, 137.9, 135.2, 129.0 (+, 2C), 127.7 (+, 2C), 126.8 (+), 124.6 (+, 2C), 114.7 (+, 2C), 64.6 (–), 59.3 (+), 55.6 (+), 49.4 (–), 35.3, 22.6 (–). FTIR (NaCl, cm^{-1}): 2961, 2866, 1661, 1510, 1454, 1400, 1250, 1157, 1055, 1031, 831, 752, 698. HRMS (TOF ES): found 332.1275, calculated for $C_{19}H_{19}NO_3Na$ (M + Na) 332.1263 (3.6 ppm).



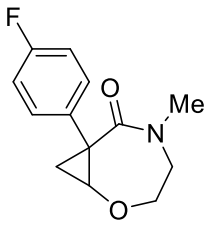
6-Benzyl-8-phenyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**199ah**). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and 3-(benzylamino)propan-1-ol (**197h**) (309 mg, 1.88 mmol, 1.5 equiv.). After extraction

and filtration through a silica plug crude *N*-benzyl-*N*-(3-hydroxypropyl)-1-phenylcycloprop-2-ene-1-carboxamide (**198ah**) was used at the cyclization step as is without additional purification. To this end, amide **198ah** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.31, mp 148-150 °C). Yield 18 mg (0.059 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.17 (m, 7H), 7.15–7.11 (m, 1H), 7.04–7.00 (m, 2H), 5.33 (dd, *J* = 14.7, 1.2 Hz, 1H), 4.16 (dd, *J* = 12.7, 5.7 Hz, 1H), 3.97 (d, *J* = 14.7 Hz, 1H), 3.87–3.76 (m, 2H), 3.67 (td, *J* = 12.8, 3.4 Hz, 1H), 3.08 (dd, *J* = 15.5, 6.7 Hz, 1H), 2.04–1.92 (m, 1H), 1.79 (dd, *J* = 7.0, 4.5 Hz, 1H), 1.46 (ddd, *J* = 15.1, 6.7, 3.3 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 139.4, 137.7, 128.9 (+, 2C), 128.7 (+, 2C), 128.6 (+, 2C), 127.6 (+), 126.6 (+), 124.8 (+, 2C), 73.4 (-), 68.8 (+), 48.9 (–), 45.7 (–), 35.9, 29.3 (–), 22.5 (–). FTIR (NaCl, cm^{-1}): 3059, 3030, 2943, 1640, 1495, 1439, 1425, 1221, 1123, 1074, 1013, 750, 698. HRMS (TOF ES): found 330.1471, calculated for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470 (0.3 ppm).



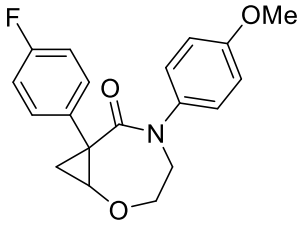
5-Benzyl-7-(4-fluorophenyl)-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199ba**). This compound was synthesized according to Typical Procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and 2-(benzylamino)ethan-1-ol (**197a**) (255 mg, 1.68 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-benzyl-1-(4-fluorophenyl)-*N*-(2-hydroxyethyl)cycloprop-2-ene-1-carboxamide (**198ba**) was used at the cyclization step as is without additional purification. To this end, amide **198ba** (20 mg, 0.064 mmol) was treated with powdered KOH (7.2 mg, 0.128 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless glass (R_f 0.44).

Yield 18 mg (0.058 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 7.12–7.04 (m, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 4.75–4.63 (m, 2H), 3.96–3.85 (m, 1H), 3.54 (dd, *J* = 11.2, 5.1 Hz, 1H), 3.44–3.34 (m, 2H), 3.05 (dd, *J* = 15.4, 4.8 Hz, 1H), 1.73 (dd, *J* = 6.9, 3.4 Hz, 1H), 1.41 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 161.8 (d, *J* = 245.8 Hz), 137.2, 133.7 (d, *J* = 3.2 Hz, +, 2C), 128.9 (+, 2C), 128.3 (+, 2C), 127.9 (+), 126.5 (d, *J* = 8.0 Hz, +, 2C), 115.9 (d, *J* = 21.4 Hz, 2C, +)., 64.4 (–), 58.5 (+), 49.9 (–), 44.9 (–), 34.4, 22.5 (–). FTIR (NaCl, cm^{-1}): 3063, 2970, 2868, 1649, 1512, 1468, 1425, 1231, 1200, 1153, 1057, 828, 698. HRMS (TOF ES): found 334.1207, calculated for $C_{19}H_{18}FNO_2Na$ (M + Na) 334.1219 (3.6 ppm).

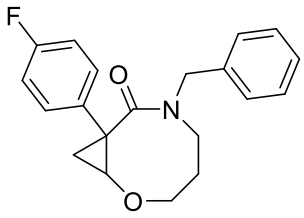


7-(4-Fluorophenyl)-5-methyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199bb**). This compound was synthesized according to Typical Procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and 2-(methylamino)ethan-1-ol (**197b**) (126 mg, 1.68 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude 1-(4-fluorophenyl)-*N*-(2-hydroxyethyl)-*N*-methylcycloprop-2-ene-1-carboxamide (**198bb**) was used at the cyclization step as is without additional purification. To this end, amide **198bb** (20 mg, 0.085 mmol) was treated with powdered KOH (9.5 mg, 0.17 mmol). The product was isolated by column chromatography eluting with EtOAc as a colorless solid (R_f 0.51, mp 104-105 °C). Yield 17.2 mg (0.073 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05–6.96 (m, 4H), 4.04 (ddd, *J* = 15.3, 12.7, 5.0 Hz, 1H), 3.86–3.76 (m, 1H), 3.69–3.61 (m, 1H), 3.38 (dd, *J* = 6.3, 3.5 Hz, 1H), 3.06 (s, 3H), 3.05–3.02 (m, 1H), 1.63 (dd, *J* = 7.0, 3.5 Hz, 1H), 1.38 (dd, *J* = 6.9, 6.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 161.8 (d, *J* = 245.6 Hz), 133.6 (d, *J* = 3.1 Hz), 126.5 (d, *J* = 8.0 Hz, +, 2C), 115.8 (d, *J* = 21.4 Hz, +, 2C), 63.3 (–), 58.4 (+), 47.5 (–), 34.4, 34.3 (+), 22.3 (–). FTIR (NaCl, cm^{-1}): 2959,

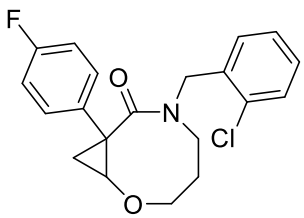
2870, 1649, 1512, 1481, 1433, 1397, 1231, 1165, 1057, 829, 791. HRMS (TOF ES): found 236.1094, calculated for $C_{13}H_{15}FNO_2$ (M + H) 236.1087 (3.0 ppm).



7-(4-Fluorophenyl)-5-(4-methoxyphenyl)-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199bg**). This compound was synthesized according to Typical Procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and 2-((4-methoxyphenyl)amino)ethan-1-ol (**197g**) (282 mg, 1.68 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude 1-(4-fluorophenyl)-*N*-(2-hydroxyethyl)-*N*-(4-methoxyphenyl)cycloprop-2-ene (**198bg**) was used at the cyclization step as is without additional purification. To this end, amide **198bg** (20 mg, 0.061 mmol) was treated with powdered KOH (6.9 mg, 0.122 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.19, mp 132-133 ^oC). Yield 18.4 mg (0.056 mmol, 92%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.23–7.18 (m, 2H), 7.17–7.12 (m, 2H), 7.07–7.01 (m, 2H), 6.95–6.90 (m, 2H), 4.32 (ddd, *J* = 15.4, 12.6, 4.9 Hz, 1H), 3.91 (td, *J* = 11.9, 4.7 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.50 (dd, *J* = 6.2, 3.5 Hz, 1H), 3.38 (dt, *J* = 19.4, 9.7 Hz, 1H), 1.79 (dd, *J* = 7.1, 3.5 Hz, 1H), 1.45 (t, *J* = 6.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 161.9 (d, *J* = 245.8 Hz), 158.5, 135.1, 133.6 (d, *J* = 3.1 Hz), 127.6 (+, 2C), 126.5 (d, *J* = 8.0 Hz, +, 2C), 115.9 (d, *J* = 21.5 Hz, +, 2C), 114.7 (+, 2C), 64.6 (–), 58.9 (+), 55.7 (+), 49.3 (–), 34.8, 22.6 (–). FTIR (NaCl, cm^{-1}): 3053, 2934, 2870, 1661, 1510, 1456, 1398, 1265, 1250, 1159, 1053, 1034, 831, 739, 704. HRMS (TOF ES): found 350.1172, calculated for $C_{19}H_{18}FNO_3Na$ (M + Na) 350.1168 (1.1 ppm).

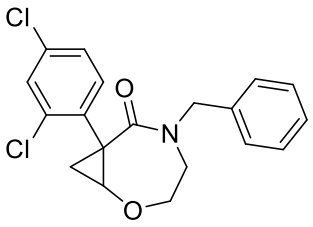


6-Benzyl-8-(4-fluorophenyl)-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**199bh**). This compound was synthesized according to Typical Procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and 3-(benzylamino)propan-1-ol (**197h**) (278 mg, 1.68 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-benzyl-1-(4-fluorophenyl)-*N*-(3-hydroxypropyl)cycloprop-2-ene-1-carboxamide (16bh) was used at the cyclization step as is without additional purification. To this end, amide **198bh** (20 mg, 0.061 mmol) was treated with powdered KOH (6.9 mg, 0.122 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.19, mp 132-133 °C). Yield 17.6 mg (0.054 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5H), 7.10–7.03 (m, 2H), 7.00–6.92 (m, 2H), 5.37 (d, *J* = 14.7 Hz, 1H), 4.22 (dd, *J* = 12.7, 5.6 Hz, 1H), 4.01 (d, *J* = 14.7 Hz, 1H), 3.90–3.80 (m, 2H), 3.73 (td, *J* = 12.7, 3.4 Hz, 1H), 3.14 (dd, *J* = 15.5, 6.7 Hz, 1H), 2.12–1.97 (m, 1H), 1.83 (dd, *J* = 7.0, 4.4 Hz, 1H), 1.54 (ddd, *J* = 15.2, 6.7, 3.2 Hz, 1H), 1.26 (dd, *J* = 9.6, 4.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 161.6 (d, *J* = 245.7 Hz), 137.6, 135.1 (d, *J* = 3.1 Hz), 128.8 (+, 2C), 128.5 (+, 2C), 127.6 (+), 126.6 (d, *J* = 7.9 Hz, +, 2C), 115.8 (d, *J* = 21.5 Hz, +, 2C), 73.4 (–), 68.5 (+), 48.9 (–), 45.7 (–), 35.4, 29.3 (–), 22.4 (–). FTIR (NaCl, cm^{-1}): 2963, 1634, 1510, 1477, 1440, 1261, 1165, 1123, 1074, 1015, 817, 752. HRMS (TOF ES): found 348.1385, calculated for $C_{20}H_{20}FNO_2Na$ (M + Na) 348.1376 (2.6 ppm).



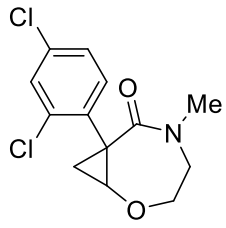
6-(2-Chlorobenzyl)-8-(4-fluorophenyl)-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**199bi**). This compound was synthesized according to Typical Procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and 3-((2-

chlorobenzyl)amino)propan-1-ol (**197i**) (336 mg, 1.68 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-(2-chlorobenzyl)-1-(4-fluorophenyl)-*N*-(3-hydroxypropyl)cycloprop-2-ene-1-carboxamide (**198bi**) was used at the cyclization step as is without additional purification. To this end, amide **198bi** (20 mg, 0.056 mmol) was treated with powdered KOH (6.2 mg, 0.112 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless glass (R_f 0.19). Yield 18.4 mg (0.051 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 1H), 7.30–7.25 (m, 1H), 7.23–7.17 (m, 2H), 7.15–7.09 (m, 2H), 7.02–6.94 (m, 2H), 5.29 (d, *J* = 15.4 Hz, 1H), 4.36 (d, *J* = 15.4 Hz, 1H), 4.24 (dd, *J* = 12.8, 5.6 Hz, 1H), 3.94 (dd, *J* = 15.6, 11.2 Hz, 1H), 3.90 (dd, *J* = 7.5, 4.4 Hz, 1H), 3.75 (tt, *J* = 14.4, 7.2 Hz, 1H), 3.15 (dd, *J* = 15.5, 6.6 Hz, 1H), 2.17–2.04 (m, 1H), 1.82 (dd, *J* = 7.0, 4.4 Hz, 1H), 1.58 (ddd, *J* = 15.1, 6.5, 3.1 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 161.7f (d, *J* = 245.7 Hz), 135.0, 134.9 (d, *J* = 3.2 Hz), 133.8, 129.9 (+), 129.6 (+), 128.8 (+), 127.2 (+), 126.9 (d, *J* = 7.8 Hz, +, 2C), 115.8 (d, *J* = 21.6 Hz, +, 2C), 73.4 (–), 68.1 (+), 46.3 (–), 46.3 (–), 35.4, 29.5 (–), 22.4 (–). FTIR (NaCl, cm^{-1}): 3066, 2945, 2922, 1638, 1510, 1474, 1439, 1304, 1223, 1165, 1121, 1074, 1021, 839, 754. HRMS (TOF ES): found 382.1001, calculated for $C_{20}H_{19}ClFNO_2Na$ (M + Na) 382.0986 (3.9 ppm).



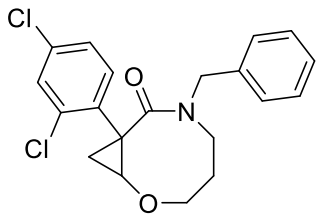
5-Benzyl-7-(2,4-dichlorophenyl)-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199ca**). This compound was synthesized according to Typical Procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**) (200 mg, 0.87 mmol, 1.0 equiv.), and 2-(benzylamino)ethan-1-ol (**197a**) (198 mg, 1.31 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-benzyl-1-(2,4-dichlorophenyl)-*N*-(2-hydroxyethyl)cycloprop-2-ene-

1-carboxamide (**198ca**) was used at the cyclization step as is without additional purification. To this end, amide **198ca** (20 mg, 0.055 mmol) was treated with powdered KOH (6.2 mg, 0.11 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless oil (R_f 0.29). Yield 16 mg (0.044 mmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 2.2 Hz, 1H), 7.31–7.19 (m, 6H), 4.81 (d, *J* = 14.8 Hz, 1H), 4.63 (ddd, *J* = 15.6, 12.4, 5.4 Hz, 1H), 4.37 (d, *J* = 14.8 Hz, 1H), 4.01 (dd, *J* = 6.3, 3.2 Hz, 1H), 3.71 (dd, *J* = 11.3, 5.3 Hz, 1H), 3.42–3.30 (m, 1H), 3.06 (dd, *J* = 15.5, 5.2 Hz, 1H), 1.72 (dd, *J* = 6.6, 3.2 Hz, 1H), 1.34 (t, *J* = 6.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 137.2, 134.7, 134.0, 133.9, 133.8 (+), 130.7 (+), 128.8 (+, 2C), 128.2 (+, 2C), 127.8 (+), 127.6 (+), 64.5 (–), 56.5 (+), 50.7 (–), 44.5 (–), 34.2, 22.4 (–). FTIR (NaCl, cm^{-1}): 3063, 2963, 1647, 1472, 1414, 1198, 1153, 1076, 1039, 787, 735, 698. HRMS (TOF ES): found 384.0522, calculated for $C_{19}H_{17}Cl_2NO_2Na$ (M + Na) 384.0534 (3.1 ppm).



7-(2,4-Dichlorophenyl)-5-methyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**199cb**). This compound was synthesized according to Typical Procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**) (200 mg, 0.87 mmol, 1.0 equiv.), and 2-(methylamino)ethan-1-ol (**197b**) (98 mg, 1.31 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude 1-(2,4-dichlorophenyl)-*N*-(2-hydroxyethyl)-*N*-methylcycloprop-2-ene-1-carboxamide (**198cb**) was used at the cyclization step as is without additional purification. To this end, amide **198cb** (20 mg, 0.07 mmol) was treated with powdered KOH (7.8 mg, 0.14 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:2) as a colorless solid (R_f 0.30, mp 139-140 °C). Yield 15.8 mg (0.055 mmol, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz,

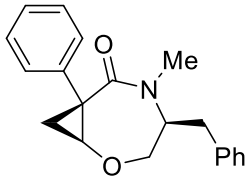
1H), 7.34 (d, *J* = 2.2 Hz, 1H), 7.21 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.82–4.69 (m, 1H), 4.01 (dd, *J* = 6.3, 3.2 Hz, 1H), 3.87–3.80 (m, 2H), 3.05 (ddd, *J* = 8.1, 5.9, 3.6 Hz, 1H), 2.97 (s, 3H), 1.62 (dd, *J* = 6.5, 3.2 Hz, 1H), 1.28 (t, *J* = 6.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 134.4, 134.0, 133.8, 133.7 (+), 130.7 (+), 127.5 (+), 63.4 (–), 56.2 (+), 46.9 (–), 35.1 (+), 34.1, 22.3 (–). FTIR (NaCl, cm^{-1}): 3003, 2962, 2926, 1647, 1474, 1435, 1395, 1253, 1215, 1169, 1107, 1080, 1040, 822, 752, 667. HRMS (TOF ES): found 308.0210, calculated for $C_{13}H_{13}Cl_2NO_2Na$ (M + Na) 308.0221 (3.6 ppm).



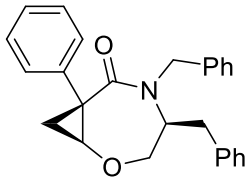
6-Benzyl-8-(2,4-dichlorophenyl)-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (**199ch**). This compound was synthesized according to Typical Procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**) (200 mg, 0.87 mmol, 1.0 equiv.), and 3-(benzylamino)propan-1-ol (**197h**) (216 mg, 1.31 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-benzyl-1-(2,4-dichlorophenyl)-*N*-(3-hydroxypropyl)cycloprop-2-ene-1-carboxamide (**198ch**) was used at the cyclization step as is without additional purification. To this end, amide **198ch** (20 mg, 0.053 mmol) was treated with powdered KOH (6 mg, 0.106 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless solid (R_f 0.37, mp 151-153 °C). Yield 17 mg (0.045 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 2.2 Hz, 1H), 7.26–7.18 (m, 4H), 7.13–7.03 (m, 2H), 5.23 (d, *J* = 15.0 Hz, 1H), 4.45–4.35 (m, 2H), 4.19 (dt, *J* = 25.4, 12.7 Hz, 1H), 4.05–3.92 (m, 2H), 3.07 (dd, *J* = 15.5, 6.6 Hz, 1H), 2.06–1.95 (m, 1H), 1.94 (dd, *J* = 6.7, 4.3 Hz, 1H), 1.94 (dd, *J* = 6.7, 4.3 Hz, 1H), 1.16–1.13 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 137.5, 134.7, 134.6, 133.9, 133.5 (+), 130.8 (+), 128.7 (+, 2C), 128.0 (+, 2C), 127.6 (+), 127.4 (+),

72.6 (–), 66.2 (+), 49.6 (–), 45.5 (–), 35.7, 29.8 (–), 21.6 (–). FTIR (NaCl, cm^{-1}): 3063, 3028, 2922, 1643, 1418, 1366, 1219, 1105, 1080, 1013, 789, 733, 698. HRMS (TOF ES): found 398.0709, calculated for $C_{20}H_{19}Cl_2NO_2Na$ (M + Na) 398.0691 (4.5 ppm).

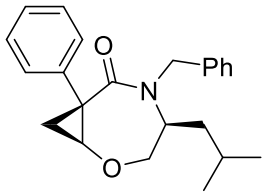
4.7.5 Cyclization of Chiral Substrates



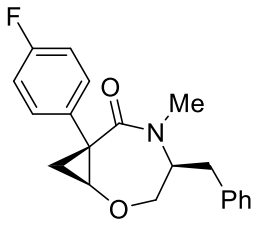
(+)-(1S,4S,7S)-4-Benzyl-5-methyl-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one ***(*****201aa*****)***. This compound was synthesized according to typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and (*S*)-2-(methylamino)-3-phenylpropan-1-ol (**214a**) (309 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude (*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-*N*-methyl-1-phenylcycloprop-2-ene-1-carboxamide (**200aa**) was used at the cyclization step as is without additional purification. To this end, amide **200aa** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless oil (R_f 0.38). Yield 18.2 mg (0.059 mmol, 91%). $[\alpha]_D^{20}$ +45.3 (c = 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.23 (m, 6H), 7.03–6.97 (m, 4H), 4.66 (dddd, *J* = 10.8, 9.6, 5.9, 4.9 Hz, 1H), 3.66–3.52 (m, 2H), 3.42 (dd, *J* = 6.2, 3.5 Hz, 1H), 2.93 (s, 3H), 2.91 (dd, *J* = 15.0, 9.6 Hz, 1H), 2.80 (dd, *J* = 14.9, 5.8 Hz, 1H), 1.71 (dd, *J* = 7.1, 3.6 Hz, 1H), 1.52 (dd, *J* = 7.1, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 137.7, 136.7, 128.8 (+, 2C), 128.8 (+, 2C), 128.6 (+, 2C), 127.0 (+), 126.9 (+), 124.7 (+, 2C), 67.6 (–), 59.8 (+), 54.8 (+), 35.1, 34.1 (–), 27.3 (+), 23.0 (–). FTIR (NaCl, cm^{-1}): 2961, 2926, 1649, 1497, 1439, 1397, 1370, 1200, 1150, 1113, 1055, 1030, 750, 696. HRMS (TOF ES): found 330.1480, calculated for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470 (3.0 ppm).



(+)-(1S,4S,7S)-4,5-Dibenzyl-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**201ab**). This compound was synthesized according to typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and (*S*)-2-(benzylamino)-3-phenylpropan-1-ol (**214b**) (452 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-*N*-(1-hydroxy-3-phenylpropan-2-yl)-1-phenylcycloprop-2-ene-1-carboxamide (**200ab**) was used at the cyclization step as is without additional purification. To this end, amide **200ab** (20 mg, 0.052 mmol) was treated with powdered KOH (5.8 mg, 0.104 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless glass (R_f 0.31). Yield 18.6 mg (0.048 mmol, 93%). $[\alpha]_D^{20}$ +67.0 (c = 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.22 (m, 11H), 7.13–7.09 (m, 2H), 7.03–6.98 (m, 2H), 5.44 (d, *J* = 15.8 Hz, 1H), 4.76 (dddd, *J* = 11.7, 9.1, 6.1, 4.5 Hz, 1H), 4.06 (d, *J* = 15.7 Hz, 1H), 3.50 (dd, *J* = 6.3, 3.6 Hz, 1H), 3.44 (dd, *J* = 11.1, 4.5 Hz, 1H), 3.07 (t, *J* = 11.4 Hz, 1H), 2.98 (dd, *J* = 15.2, 9.2 Hz, 1H), 2.69 (dd, *J* = 15.2, 6.1 Hz, 1H), 1.90 (dd, *J* = 7.1, 3.5 Hz, 1H), 1.58 (dd, *J* = 7.1, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 138.9, 137.7, 136.9, 128.9 (+, 2C), 128.9 (+, 2C), 128.7 (+, 2C), 128.3 (+, 2C), 127.5 (+, 2C), 127.4 (+), 127.0 (+), 127.0 (+), 124.9 (+, 2C), 69.5 (–), 59.9 (+), 54.8 (+), 44.8 (–), 35.2, 33.5 (–), 23.3 (–). FTIR (NaCl, cm^{-1}): 3059, 3026, 2964, 1649, 1497, 1408, 1377, 1207, 1055, 1028, 746, 696. HRMS (TOF ES): found 406.1770, calculated for $C_{26}H_{25}NO_2Na$ (M + Na) 406.1783 (3.2 ppm).

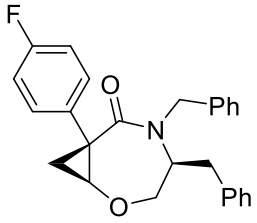


(+)-(1S,4S,7S)-5-Benzyl-4-isobutyl-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**201ad**). This compound was synthesized according to typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and (*S*)-2-(benzylamino)-4-methylpentan-1-ol (**214d**) (388 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-*N*-(1-hydroxy-4-methylpentan-2-yl)-1-phenylcycloprop-2-ene-1-carboxamide (**200ad**) was used at the cyclization step as is without additional purification. To this end, amide **200ad** (20 mg, 0.057 mmol) was treated with powdered KOH (6.4 mg, 0.114 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.38, mp 117-118 °C). Yield 18.8 mg (0.054 mmol, 94%). $[\alpha]_D^{20}$ +83.4 (c = 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.20 (m, 8H), 7.12–7.07 (m, 2H), 5.39 (d, *J* = 15.7 Hz, 1H), 4.37–4.25 (m, 1H), 4.12 (d, *J* = 15.5 Hz, 1H), 3.46 (dd, *J* = 6.2, 3.6 Hz, 1H), 3.35 (dd, *J* = 11.1, 4.5 Hz, 1H), 2.99–2.87 (m, 1H), 1.86 (dd, *J* = 7.1, 3.5 Hz, 1H), 1.65 (ddd, *J* = 14.2, 9.7, 4.4 Hz, 1H), 1.57 (dd, *J* = 7.1, 6.3 Hz, 1H), 1.55–1.46 (m, 1H), 0.98 (ddd, *J* = 14.3, 9.0, 4.4 Hz, 1H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.63 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 138.9, 137.9, 128.9 (+, 2C), 128.6 (+, 2C), 127.7 (+, 2C), 127.3 (+), 126.8 (+), 124.6 (+, 2C), 69.6 (–), 60.0 (+), 52.9 (+), 44.7 (–), 36.3 (–), 35.2, 25.3 (+), 23.2 (–), 23.1 (+), 21.7 (+). FTIR (NaCl, cm^{-1}): 2955, 2925, 2866, 1647, 1497, 1437, 1410, 1377, 1219, 1172, 1055, 1029, 748, 698. HRMS (TOF ES): found 372.1926, calculated for $C_{23}H_{27}NO_2Na$ (M + Na) 372.1939 (3.5 ppm).



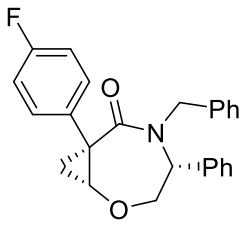
(+)-(1S,4S,7S)-4-Benzyl-7-(4-fluorophenyl)-5-methyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (201ba). This compound was synthesized according to typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-

carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and (*S*)-2-(methylamino)-3-phenylpropan-1-ol (**214a**) (278 mg, 1.68 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude (*S*)-1-(4-fluorophenyl)-N-(1-hydroxy-3-phenylpropan-2-yl)-N-methylcycloprop-2-ene-1-carboxamide (**200ba**) was used at the cyclization step as is without additional purification. To this end, amide **200ba** (20 mg, 0.061 mmol) was treated with powdered KOH (6.8 mg, 0.122 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless oil (R_f 0.1). Yield 19.2 mg (0.059 mmol, 96%). $[\alpha]_D^{20}$ +41.0 (c = 0.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.22 (m, 3H), 7.04–6.92 (m, 6H), 4.70–4.53 (m, 1H), 3.68–3.51 (m, 2H), 3.39 (dd, *J* = 6.3, 3.5 Hz, 1H), 2.98–2.89 (m,1H), 2.92 (s, 3H), 2.80 (dd, *J* = 14.9, 5.8 Hz, 1H), 1.69 (dd, *J* = 7.2, 3.5 Hz, 1H), 1.45 (dd, *J* = 7.2, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 161.9 (d, *J* = 245.6 Hz), 136.7, 133.4 (d, *J* = 3.1 Hz), 128.8 (+, 2C), 128.5 (+, 2C), 127.1 (+), 126.4 (d, *J* = 7.9 Hz, +, 2C), 115.7 (d, *J* = 21.4 Hz, +, 2C), 67.5 (–), 59.5 (+), 55.1 (+), 34.6, 34.1 (–), 27.3 (+), 23.0 (–). FTIR (NaCl, cm^{-1}): 2961, 2920, 2866, 1647, 1515, 1454, 1425, 1398, 1368, 1230, 1165, 1111, 1049, 831, 812, 793, 700. HRMS (TOF ES): found 348.1390, calculated for $C_{20}H_{20}FNO_2Na$ (M + Na) 348.1376 (4.0 ppm).



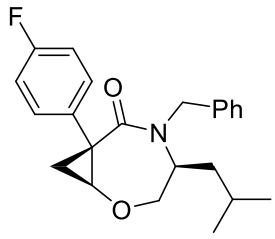
(+)-(1S,4S,7S)-4,5-Dibenzyl-7-(4-fluorophenyl)-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**201bb**). This compound was synthesized according to typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and (*S*)-2-(benzylamino)-3-phenylpropan-1-ol (**214b**) (406 mg, 1.68 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-1-(4-fluorophenyl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)cycloprop-2-ene-1-carboxamide (**200bb**) was used at the cyclization step as is

without additional purification. To this end, amide **200bb** (20 mg, 0.05 mmol) was treated with powdered KOH (5.6 mg, 0.1 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless glass (R_f 0.31). Yield 18 mg (0.045 mmol, 90%). $[\alpha]_D^{20}$ +53.0 (c = 0.90, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 4H), 7.28–7.22 (m, 4H), 7.11–7.02 (m, 4H), 6.99 (dd, *J* = 7.4, 2.1 Hz, 2H), 5.41 (d, *J* = 15.7 Hz, 1H), 4.71 (dddd, *J* = 11.8, 9.0, 6.2, 4.5 Hz, 1H), 4.06 (d, *J* = 15.7 Hz, 1H), 3.48 (dd, *J* = 6.4, 3.6 Hz, 1H), 3.44 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.07 (t, *J* = 11.4 Hz, 1H), 2.99 (dd, *J* = 15.1, 9.0 Hz, 1H), 2.69 (dd, *J* = 15.1, 6.2 Hz, 1H), 1.87 (dd, *J* = 7.2, 3.5 Hz, 1H), 1.50 (dd, *J* = 7.1, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 161.9 (d, *J* = 245.8 Hz), 138.8, 136.9, 133.5 (d, *J* = 3.2 Hz), 129.0 (+, 2C), 128.7 (+, 2C), 128.3 (+, 2C), 127.5 (+), 127.4 (+, 2C), 127.1 (+), 126.6 (d, *J* = 7.9 Hz, +, 2C), 115.8 (d, *J* = 21.7 Hz, +, 2C), 69.5 (–), 59.5 (+), 55.0 (+), 44.9 (–), 34.7, 33.6 (–), 23.3 (–). FTIR (NaCl, cm^{-1}): 2965, 2864, 1649, 1512, 1416, 1233, 1165, 750, 698. HRMS (TOF ES): found 424.1707, calculated for C26H24FNO2Na (M + Na) 424.1689 (4.2 ppm).

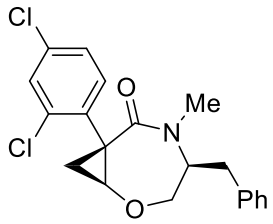


(–)-(1R,4R,7R)-5-Benzyl-7-(4-fluorophenyl)-4-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**201bc**). This compound was synthesized according to typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and (*R*)-2-(benzylamino)-2-phenylethan-1-ol (**214c**) (383 mg, 1.68 mmol, 1.5 equiv.). After extraction the (*R*)-*N*-benzyl-1-(4-fluorophenyl)-*N*-(2-hydroxy-1-phenylethyl)cycloprop-2-ene-1-carboxamide (**200bc**) was isolated by column chromatography eluting with a dichloromethane/EtOAc mixture (3:1) as a mixture of rotamers in a ratio of 2.2 : 1 as a colorless solid (R_f 0.33, mp 158-159 °C). Yield 146.7 mg (0.38 mmol, 34%). $[\alpha]_D^{20}$ –28.3 (c = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ

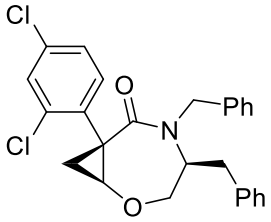
[7.44–7.20 (m), Σ8H], [7.10–7.06 (m), 7.01–6.92 (m), 6.80 (br. m), Σ6H], [5.48–5.42 (m), 5.22 (dd, *J* = 8.4, 4.6 Hz), Σ1H], [5.11 (d, *J* = 15.1 Hz), 4.42 (d, *J* = 16.9 Hz), 4.20 (d, *J* = 16.9 Hz), 3.87 (d, *J* = 15.0 Hz), Σ2H], [4.15–4.08 (m), 4.06–4.00 (m), 3.81–3.65 (br. m), 3.63–3.55 (br. m), Σ2H], [1.72 (br.s), 1.40 (br. s), Σ1H]. ^{13}C NMR (126 MHz, $CDCl_3$) δ Major diastereomer: 176.9, 161.8 (d, *J* = 245.4 Hz), 138.4 (d, *J* = 2.7 Hz), 137.7, 137.0, 128.8 (+, 4C), 128.5 (+, 2C), 128.2 (+),127.8 (d, *J* = 7.8 Hz, +, 2C), 127. 6 (+), 126.8 (+, 2C), 115.5 (d, *J* = 21.2 Hz, +, 2C), 110.2 (+), 109.8 (+), 63.9 (–), 63.1 (+), 50.6 (–), 32.6. Minor diastereomer: 176.1, 161.9 (d, *J* = 246.1 Hz), 139.3, 139.0 (d, *J* = 2.6 Hz), 136.6, 128.9 (+, 4C), 128.1 (+), 127.8 (+, 2C), 127.5 (+), 128.4 (d, *J* = 7.9 Hz, +, 2C), 127.6 (+, 2C), 115.5 (d, *J* = 21.2 Hz, +, 2C), 111.7 (+), 110.4 (+), 62.5 (+), 62.4 (–), 45.7 (–), 29.8. FTIR (NaCl, cm^{-1}): 3366 (br), 3063, 3030, 2916, 1605, 1508, 1452, 1414, 1231, 1159, 829, 752, 700, 621. HRMS (TOF ES): found 410.1512, calculated for $C_{25}H_{22}FNO_2Na$ (M + Na) 410.1532 (4.9 ppm). To this end, amide **200bc** (20 mg, 0.052 mmol) was treated with powdered KOH (5.8 mg, 0.104 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.4, mp 192-194 °C). Yield 17.8 mg (0.046 mmol, 89%). $[\alpha]_D^{20}$ –82.6 (c = 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.31 (m, 1H), 7.32–7.26 (m, 2H), 7.19–7.16 (m, 5H), 7.12–7.06 (m, 2H), 6.96–6.89 (m, 4H), 5.46 (dd, *J* = 11.7, 5.1 Hz, 1H), 5.04 (d, *J* = 15.3 Hz, 1H), 3.82–3.71 (m, 3H), 3.52 (dd, *J* = 6.3, 3.5 Hz, 1H), 1.92 (dd, *J* = 7.2, 3.5 Hz, 1H), 1.59 (dd, *J* = 7.2, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 161.9 (d, *J* = 245.8 Hz), 138.3, 133.9 (d, *J* = 3.0 Hz), 132.6, 129.7 (+, 2C), 129.3 (+), 128.9 (+, 2C), 128.2 (+, 2C), 127.7 (+, 2C), 127.1 (+), 126.3 (d, *J* = 7.9 Hz, +, 2C), 116.1 (d, *J* = 21.5 Hz, +, 2C), 67.2 (–), 59.9 (+), 58.5 (+), 45.6 (–), 34.7, 23.2 (–). FTIR (NaCl, cm^{-1}): 3032, 2926, 2862, 1651, 1510, 1416, 1402, 1223, 1165, 1030, 831, 802, 750, 698. HRMS (TOF ES): found 410.1539, calculated for $C_{25}H_{22}FNO_2Na$ (M + Na) 410.1532 (1.7 ppm).



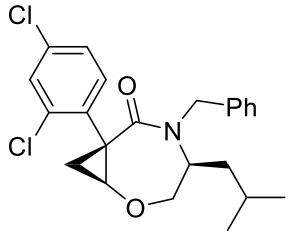
(+)-(1S,4S,7S)-5-Benzyl-7-(4-fluorophenyl)-4-isobutyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**201bd**). This compound was synthesized according to typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and (*S*)-2-(benzylamino)-4-methylpentan-1-ol (**214d**) (349 mg, 1.68 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-1-(4-fluorophenyl)-*N*-(1-hydroxy-4-methylpentan-2-yl)cycloprop-2-ene-1-carboxamide (**200bd**) was used at the cyclization step as is without additional purification. To this end, amide **200bd** (20 mg, 0.054 mmol) was treated with powdered KOH (6.1 mg, 0.108 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.35, mp 139-141 °C). Yield 18.6 mg (0.05 mmol, 93%). $[\alpha]_D^{20}$ +79.3 (c = 0.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.21 (m, 5H), 7.12–7.06 (m, 2H), 7.05–6.99 (m, 2H), 5.37 (d, *J* = 15.5 Hz, 1H), 4.29 (ddt, *J* = 11.9, 9.2, 4.5 Hz, 1H), 4.10 (d, *J* = 15.5 Hz, 1H), 3.45 (dd, *J* = 6.3, 3.5 Hz, 1H), 3.36 (dd, *J* = 11.0, 4.5 Hz, 1H), 2.99–2.89 (m, 1H), 1.84 (dd, *J* = 7.1, 3.5 Hz, 1H), 1.65 (ddd, *J* = 14.2, 9.4, 4.6 Hz, 1H), 1.56–1.46 (m, 1H), 1.49 (dd, *J* = 7.1, 6.3 Hz, 1H), 1.00 (ddd, *J* = 14.4, 9.0, 4.5 Hz, 1H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.65 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 161.8 (d, *J* = 245.6 Hz), 138.7, 133.7 (d, *J* = 3.2 Hz), 128.6 (+, 2C), 127.7 (+, 2C), 127.4 (+), 126.4 (d, *J* = 7.9 Hz, +, 2C), 115.8 (d, *J* = 21.5 Hz, +, 2C), 69.6 (–), 59.5 (+), 52.9 (+), 44.7 (–), 36.2 (–), 34.7, 25.3 (+), 23.3 (–), 23.0 (+), 21.8 (+). FTIR (NaCl, cm^{-1}): 2955, 2868, 1647, 1512, 1417, 1352, 1223, 1159, 1030, 835, 799, 727, 700. HRMS (TOF ES): found 368.2028, calculated for $C_{23}H_{27}FNO_2$ (M + H) 368.2026 (0.5 ppm). The relative and absolute configuration of compound **201bd** was unambiguously confirmed by single-crystal X-ray crystallography (CCDC #1823183).



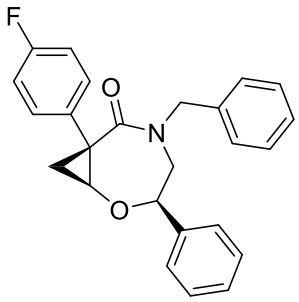
(+)-(1S,4S,7S)-4-Benzyl-7-(2,4-dichlorophenyl)-5-methyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**201ca**). This compound was synthesized according to typical procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**) (200 mg, 0.87 mmol, 1.0 equiv.), and (*S*)-2-(methylamino)-3-phenylpropan-1-ol (**214a**) (216 mg, 1.31 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude (*S*)-1-(2,4-dichlorophenyl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-*N*-methylcycloprop-2-ene-1-carboxamide (**200ca**) was used at the cyclization step as is without additional purification. To this end, amide **200ca** (20 mg, 0.053 mmol) was treated with powdered KOH (5.9 mg, 0.106 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless oil (R_f 0.5). Yield 16.8 mg (0.045 mmol, 84%). $[\alpha]_D^{20}$ +36.5 (c = 0.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.31–7.19 (m, 4H), 7.15–7.10 (m, 2H), 5.15 (ddt, *J* = 11.9, 7.7, 3.8 Hz, 1H), 4.07 (dd, *J* = 6.3, 3.2 Hz, 1H), 3.75 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.54 (t, *J* = 11.3 Hz, 1H), 3.04 (dd, *J* = 14.3, 7.7 Hz, 1H), 2.88 (s, 3H), 2.83 (dd, *J* = 14.3, 7.7 Hz, 1H), 1.66 (dd, *J* = 6.7, 3.2 Hz, 1H), 1.39 (t, *J* = 6.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 136.9, 133.9, 133.9, 133.7 (+), 133.5, 130.7 (+), 128.9 (+, 2C), 128.7 (+, 2C), 127.6 (+), 127.1 (+), 67.5 (–), 56.9 (+), 54.4 (+), 35.0 (–), 34.6, 28.2 (+), 22.9 (–). FTIR (NaCl, cm^{-1}): 3005, 2924, 2866, 1645, 1474, 1397, 1366, 1200, 1152, 1107, 1069, 1032, 829, 754, 698. HRMS (TOF ES): found 398.0704, calculated for $C_{20}H_{19}Cl_2NO_2Na$ (M + Na) 398.0691 (3.3 ppm).



(+)-(1S,4S,7S)-4,5-Dibenzyl-7-(2,4-dichlorophenyl)-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**201cb**). This compound was synthesized according to typical procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**) (200 mg, 0.87 mmol, 1.0 equiv.), and (*S*)-2-(benzylamino)-3-phenylpropan-1-ol (**214b**) (316 mg, 1.31 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-1-(2,4-dichlorophenyl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)cycloprop-2-ene-1-carboxamide (**200cb**) was used at the cyclization step as is without additional purification. To this end, amide **200cb** (20 mg, 0.044 mmol) was treated with powdered KOH (4.9 mg, 0.088 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless oil (R_f 0.44). Yield 17.4 mg (0.038 mmol, 87%). $[\alpha]_D^{20}$ +56.6 (c = 0.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.34–7.19 (m, 9H), 7.13–7.07 (m, 2H), 5.26 (dt, *J* = 7.9, 4.0 Hz, 1H), 5.20 (d, *J* = 15.8 Hz, 1H), 4.16 (d, *J* = 15.7 Hz, 1H), 4.10 (dd, *J* = 6.3, 3.3 Hz, 1H), 3.64 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.13 (t, *J* = 11.3 Hz, 1H), 3.08 (dd, *J* = 14.4, 7.3 Hz, 1H), 2.76 (dd, *J* = 14.4, 7.9 Hz, 1H), 1.82 (dd, *J* = 6.6, 3.2 Hz, 1H), 1.43 (t, *J* = 6.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 138.7, 137.0, 134.1, 134.0 (+), 133.7, 130.7 (+), 129.0 (+, 2C), 128.7 (+, 2C), 128.5 (+, 2C), 127.7 (+), 127.4 (+, 2C), 127.4 (+), 127.1 (+), 69.2 (–), 57.3 (+), 54.4 (+), 45.6 (–), 34.6, 34.5 (–), 23.3 (–). FTIR (NaCl, cm^{-1}): 3026, 2926, 1647, 1495, 1473, 1406, 1371, 1244, 1030, 752, 698. HRMS (TOF ES): found 452.1195, calculated for $C_{26}H_{24}Cl_2NO_2$ (M + H) 452.1184 (2.4 ppm).

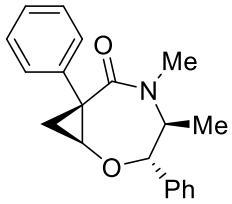


(+)-(1S,4S,7S)-5-Benzyl-7-(2,4-dichlorophenyl)-4-isobutyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**201cd**). This compound was synthesized according to typical procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**) (200 mg, 0.87 mmol, 1.0 equiv.), and (*S*)-2-(benzylamino)-4-methylpentan-1-ol (**214d**) (272 mg, 1.31 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-1-(2,4-dichlorophenyl)-*N*-(1-hydroxy-4-methylpentan-2-yl)cycloprop-2-ene-1-carboxamide (**200cd**) was used at the cyclization step as is without additional purification. To this end, amide **200cd** (20 mg, 0.048 mmol) was treated with powdered KOH (5.4 mg, 0.096 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.53, mp 144-146 °C). Yield 18 mg (0.043 mmol, 90%). $[\alpha]_D^{20}$ +77.6 (c = 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 2.2 Hz, 1H), 7.28–7.19 (m, 6H), 5.28 (d, *J* = 15.6 Hz, 1H), 4.87 (ddt, *J* = 11.7, 9.5, 4.8 Hz, 1H), 4.15 (dd, *J* = 6.3, 3.2 Hz, 1H), 4.02 (d, *J* = 15.6 Hz, 1H), 3.60 (dd, *J* = 11.2, 4.7 Hz, 1H), 2.97 (t, *J* = 11.4 Hz, 1H), 1.81 (dd, *J* = 6.7, 3.2 Hz, 1H), 1.66 (ddd, *J* = 14.1, 9.1, 5.0 Hz, 1H), 1.62–1.50 (m, 1H), 1.41 (t, *J* = 6.5 Hz, 1H), 1.12 (ddd, *J* = 13.8, 8.6, 5.0 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 138.7, 134.2, 133.9, 133.6, 133.6 (+), 130.8 (+), 128.6 (+, 2C), 127.5 (+, 3C), 127.3 (+), 69.6 (–), 57.2 (+), 52.1 (+), 45.2 (–), 36.7 (–), 34.4, 25.4 (+), 23.2 (–), 23.2 (+), 22.3 (+). FTIR (NaCl, cm^{-1}): 3063, 3957, 3868, 1647, 1473, 1404, 1371, 1217, 1028, 868, 804, 748, 731, 696. HRMS (TOF ES): found 440.1143, calculated for $C_{23}H_{25}Cl_2NO_2Na$ (M + Na) 440.1160 (3.9 ppm).

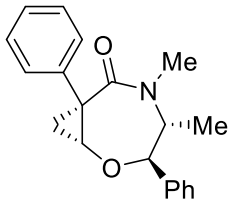


(1S,3R,7S)- and (1R,3R,7R)-5-benzyl-7-(4-fluorophenyl)-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**204b** and **205b**). These compounds were synthesized according to typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and (*R*)-2-(benzylamino)-1-phenylethan-1-ol (**215**) (383 mg, 1.68 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude (*R*)-*N*-benzyl-1-(4-fluorophenyl)-*N*-(2-hydroxy-2-phenylethyl)cycloprop-2-ene-1-carboxamide (**203b**) was used at the cyclization step as is without additional purification. To this end, amide **203b** (20 mg, 0.052 mmol) was treated with powdered KOH (5.8 mg, 0.104 mmol). The reaction mixture was vigorously stirred at 50 °C for 48 h,. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a mixture of diastereomers in a ratio of 4 : 1 as a colorless oil (R_f 0.30). Yield 18.8 mg (0.049 mmol, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ Major diastereomer: 7.43–7.19 (m, 10H), 7.12–7.03 (m, 2H), 7.03–6.95 (m, 2H), 4.79 (dd, *J* = 32.0, 14.8 Hz, 2H), 4.54 (dd, *J* = 11.6, 4.4 Hz, 1H), 4.10 (dd, *J* = 15.2, 11.5 Hz, 1H), 3.58 (dd, *J* = 6.3, 3.5 Hz, 1H), 3.47 (dd, *J* = 15.3, 4.5 Hz, 1H), 1.79 (dd, *J* = 6.9, 3.5 Hz, 1H), 1.42 (t, *J* = 6.6 Hz, 1H). Minor diastereomer: 7.43–7.19 (m, 10H), 7.12–7.03 (m, 2H), 7.03–6.95 (m, 1H), 6.92–6.90 (m, 1H), 5.37 (d, *J* = 14.8 Hz, 1H), 4.85 (d, *J* = 4.7 Hz, 1H) , 4.15 (dd, *J* = 15.0, 4.6 Hz, 1H) , 3.71 (dd, *J* = 6.2, 3.5 Hz, 1H) , 3.16 (d, *J* = 15.3 Hz, 1H), 2.82 (d, *J* = 14.8 Hz, 1H), 1.95 (dd, *J* = 7.0, 3.4 Hz, 1H) , 1.53 (dd, *J* = 7.1, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ Major diastereomer: 170.6, 161.8 (d, *J* = 245.8 Hz), 137.5, 137.1, 133.5 (d, *J* = 3.2 Hz), 129.0 (+, 2C), 129.0 (+, 2C), 128.4 (+), 128.4 (+, 2C), 128.0 (+), 126.7 (d, *J* = 8.1 Hz, +,2C), 126.4 (+, 2C), 115.9 (d, *J* = 21.6 Hz, +, 2C), 74.3 (+), 55.1 (+), 50.2 (–), 48.5 (–), 34.5, 22.4 (–). Minor diastereomer: 170.5, 161.8 (d, *J* = 246.1 Hz), 140.0, 137.0, 133.7 (d, *J* = 3.2 Hz), 128.7 (+, 2C), 128.7 (+, 2C), 128.3 (+, 2C), 128.2

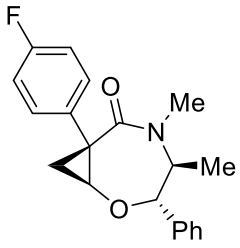
(+), 127.7 (+), 126.5 (d, *J* = 7.9 Hz, +, 2C), 125.8 (+, 2C), 115.9 (d, *J* = 21.4 Hz, +, 2C), 75.8 (+), 59.1 (+), 50.7 (–), 50.5 (–), 34.5, 22.7 (–). HRMS (TOF ES): found 410.1529, calculated for $C_{25}H_{22}FNO_2Na$ (M + Na) 410.1532 (0.7 ppm).



(–)-(1S,3S,4S,7S)-4,5-Dimethyl-3,7-diphenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**207a**). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride (**214**) (378 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-1-phenylcycloprop-2-ene-1-carboxamide (**206a**) was used at the cyclization step as is without additional purification. To this end, amide **206a** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:2) as a colorless glass (R_f 0.28). Yield 17.2 mg (0.056 mmol, 86%). $[\alpha]_D^{20}$ –55.3 (c = 0.80, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.32 (m, 5H), 7.29–7.24 (m, 3H), 7.14–7.07 (m, 2H), 4.70 (dq, *J* = 10.8, 6.9 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 3.68 (dd, *J* = 6.4, 3.6 Hz, 1H), 3.08 (s, 3H), 1.71 (dd, *J* = 6.8, 3.5 Hz, 1H), 1.44 (t, *J* = 6.7 Hz, 1H), 1.12 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 138.2, 136.6, 129.2 (+, 2C), 129.1 (+, 2C), 129.1 (+), 128.5 (+, 2C), 126.8 (+), 124.5 (+, 2C), 80.1 (+), 55.7 (+), 51.5 (+), 35.1, 27.6 (+), 23.4 (–), 15.1 (+). FTIR (NaCl, cm^{-1}): 2983, 2920, 1646, 1495, 1452, 1425, 1397, 1152, 1049, 1018, 762, 698. HRMS (TOF ES): found 330.1469, calculated for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470 (0.3 ppm).

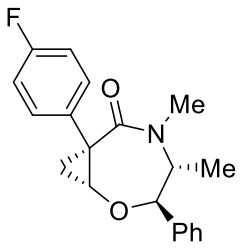


(+)-(1R,3R,4R,7R)-4,5-Dimethyl-3,7-diphenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (*ent*-**207a**). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and (1R,2R)-(–)-pseudoephedrine hydrochloride (*ent*-**214**) (378 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-1-phenylcycloprop-2-ene-1-carboxamide (*ent*-**206a**)was used at the cyclization step as is without additional purification. To this end, amide *ent*-**206a** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:2) as a colorless glass (R_f 0.28). $[\alpha]_D^{20}$ +55.9 (c = 0.80, $CHCl_3$). Yield 17.6 mg (0.057 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.32 (m, 5H), 7.30–7.25 (m, 3H), 7.14–7.10 (m, 2H), 4.70 (dq, *J* = 10.8, 7.0 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 3.68 (dd, *J* = 6.4, 3.5 Hz, 1H), 3.08 (s, 3H), 1.71 (dd, *J* = 6.9, 3.5 Hz, 1H), 1.44 (t, *J* = 6.7 Hz, 1H), 1.12 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 138.2, 136.6, 129.2 (+, 2C), 129.1 (+, 2C), 129.1 (+), 128.5 (+, 2C), 126.8 (+), 124.5 (+, 2C), 80.1 (+), 55.7 (+), 51.5 (+), 35.1, 27.6 (+), 23.4 (–), 15.1 (+). FTIR (NaCl, cm^{-1}): 2984, 2923, 1645, 1495, 1454, 1427, 1397, 1152, 1049, 1018, 762, 698. HRMS (TOF ES): found 330.1467, calculated for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470 (0.9 ppm).



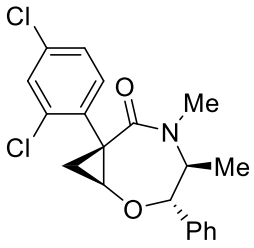
(–)-(1S,3S,4S,7S)-7-(4-Fluorophenyl)-4,5-dimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**207b**). This compound was synthesized according to Typical Procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride (**214**) (340 mg, 1.68 mmol, 1.5 equiv.). After extraction and

filtration through a silica plug crude 1-(4-fluorophenyl)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylcycloprop-2-ene-1-carboxamide (**206b**) was used at the cyclization step as is without additional purification. To this end, amide **206b** (20 mg, 0.061 mmol) was treated with powdered KOH (6.8 mg, 0.122 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:1) as a colorless solid (R_f 0.60, mp 73-75 °C). $[\alpha]_D^{20}$ –49.5 (c = 0.80, $CHCl_3$). Yield 18.6 mg (0.057 mmol, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 5.7, 1.6 Hz, 3H), 7.26 (s, 2H), 7.12–7.03 (m, 4H), 4.67 (dq, *J* = 10.8, 6.9 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 3.64 (dd, *J* = 6.5, 3.5 Hz, 1H), 3.07 (s, 3H), 1.70 (dd, *J* = 6.9, 3.5 Hz, 1H), 1.38 (t, *J* = 6.7 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 161.8 (d, *J* = 245.6 Hz), 136.4, 133.9 (d, *J* = 3.0 Hz), 129.2 (+, 2C), 129.1 (+), 128.4 (+, 2C), 126.2 (d, *J* = 8.0 Hz, +, 2C), 116.1 (d, *J* = 21.4 Hz, +, 2C), 80.0 (+), 55.4 (+), 51.5 (+), 34.6, 27.6 (+), 23.3 (–), 15.1 (+). FTIR (NaCl, cm^{-1}): 2989, 1647, 1510, 1397, 1233, 1152, 1098, 1044, 1017, 829, 804, 762, 702, 637. HRMS (TOF ES): found 348.1383, calculated for $C_{20}H_{20}FNO_2Na$ (M + Na) 348.1376 (2.0 ppm).



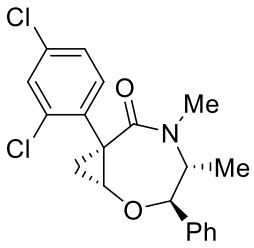
(+)-(1R,3R,4R,7R)-7-(4-Fluorophenyl)-4,5-dimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one *(ent-***207b***)*. This compound was synthesized according to Typical Procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**196b**) (200 mg, 1.12 mmol, 1.0 equiv.), and (1*R*,2*R*)-(–)-pseudoephedrine hydrochloride (*ent*-**214**) (340 mg, 1.68 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude 1-(4-fluorophenyl)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylcycloprop-2-ene-1-carboxamide (*ent*-**206b**) was used at the cyclization step as is without additional purification. To this end, amide *ent*-**206b** (20 mg, 0.061 mmol) was treated with powdered KOH (6.8 mg, 0.122 mmol). The product was isolated by column chromatography

eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.14, mp 74-76 ºC). $[\alpha]_D^{20}$ +50.3 (c = 0.90, $CHCl_3$). Yield 19.2 mg (0.059 mmol, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.35 (m, 3H), 7.28–7.24 (m, 2H), 7.12–7.02 (m, 4H), 4.67 (dq, *J* = 10.8, 7.0 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 3.64 (dd, *J* = 6.4, 3.5 Hz, 1H), 3.07 (s, 3H), 1.69 (dd, *J* = 6.9, 3.5 Hz, 1H), 1.38 (t, *J* = 6.7 Hz, 1H), 1.13 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 161.8 (d, *J* = 245.6 Hz), 136.4, 133.9 (d, *J* = 3.1 Hz), 129.2 (+, 2C), 129.1 (+), 128.4 (+, 2C), 126.2 (d, *J* = 7.8 Hz, +, 2C), 116.1 (d, *J* = 21.6 Hz, +, 2C), 80.0 (+), 55.4 (+), 51.5 (+), 34.6, 27.6 (+), 23.3 (–), 15.1 (+). FTIR (NaCl, cm^{-1}): 2986, 1647, 1510, 1397, 1233, 1152, 1046, 1018, 831, 804, 760, 702, 637. HRMS (TOF ES): found 348.1382, calculated for $C_{20}H_{20}FNO_2Na$ (M + Na) 348.1376 (1.7 ppm).



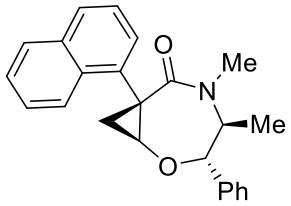
(–)-(1S,3S,4S,7S)-7-(2,4-Dichlorophenyl)-4,5-dimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**207c**). This compound was synthesized according to Typical Procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**) (200 mg, 0.87 mmol, 1.0 equiv.), and (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride (**214**) (264 mg, 1.31 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude 1-(2,4-dichlorophenyl)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylcycloprop-2-ene-1-carboxamide (**206c**) was used at the cyclization step as is without additional purification. To this end, amide **206c** (20 mg, 0.053 mmol) was treated with powdered KOH (5.9 mg, 0.106 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.54, mp 144-146 ºC). Yield 16.4 mg (0.043 mmol, 82%). $[\alpha]_D^{20}$ –85.2 (c = 0.70, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.5 Hz, 1H), 7.48–7.40 (m, 5H), 7.39 (d, *J* = 2.3 Hz, 1H), 7.28–7.24 (m, 1H), 5.16 (dq, *J* = 10.8, 7.0 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 4.22 (dd, *J* = 6.3, 3.2 Hz,

1H), 2.99 (s, 3H), 1.69 (dd, *J* = 6.7, 3.2 Hz, 1H), 1.54 (t, *J* = 6.5 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 136.9, 134.1, 133.8, 133.7, 132.2 (+), 131.2 (+), 129.2 (+, 2C), 129.1 (+), 128.5 (+, 2C), 127.6 (+), 80.1 (+), 53.6 (+), 51.3 (+), 34.6, 27.9 (+), 22.3 (–), 15.1 (+). FTIR (NaCl, cm^{-1}): 2922, 2851, 1653, 1471, 1392, 1152, 1107, 1068, 758, 702. HRMS (TOF ES): found 376.0854, calculated for $C_{20}H_{20}Cl_2NO_2$ (M + H) 376.0871 (4.5 ppm). The relative and absolute configuration of compound **207c** was unambiguously confirmed by single-crystal X-ray crystallography (CCDC # 1823195).

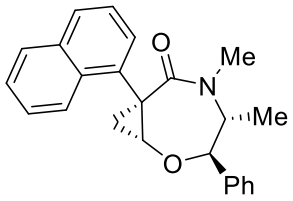


(+)-(1R,3R,4R,7R)-7-(2,4-Dichlorophenyl)-4,5-dimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one *(ent-***207c***).* This compound was synthesized according to typical procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**) (200 mg, 0.87 mmol, 1.0 equiv.), and (1*R*,2*R*)-(–)-pseudoephedrine hydrochloride (*ent*-**214**) (264 mg, 1.31 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude 1-(2,4-dichlorophenyl)-N-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-N-methylcycloprop-2-ene-1-carboxamide (*ent*-**206c**) was used at the cyclization step as is without additional purification. To this end, amide *ent*-**206c** (20 mg, 0.053 mmol) was treated with powdered KOH (5.9 mg, 0.106 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.54, mp 140-141 ºC). Yield 16.8 mg (0.045 mmol, 84%). $[\alpha]_D^{20}$ +81.8 (c = 0.70, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.5 Hz, 1H), 7.47–7.40 (m, 5H), 7.39 (d, *J* = 2.3 Hz, 1H), 7.30–7.24 (m, 1H), 5.16 (dq, *J* = 10.9, 7.0 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 4.22 (dd, *J* = 6.3, 3.1 Hz, 1H), 2.99 (s, 3H), 1.69 (dd, *J* = 6.7, 3.2 Hz, 1H), 1.54 (t, *J* = 6.5 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 136.9, 134.1, 133.8, 133.7, 132.2 (+), 131.2

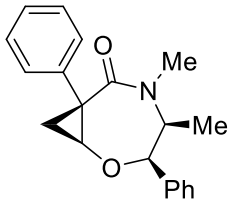
(+), 129.2 (+, 2C), 129.1 (+), 128.5 (+, 2C), 127.6 (+), 80.0 (+), 53.6 (+), 51.3 (+), 34.6, 27.9 (+), 22.3 (–), 15.1 (+). FTIR (NaCl, cm^{-1}): 2922, 2851, 1653, 1474, 1392, 1152, 1107, 1068, 760, 700. HRMS (TOF ES): found 398.0702, calculated for $C_{20}H_{19}Cl_2NO_2Na$ (M + Na) 398.0691 (2.8 ppm).



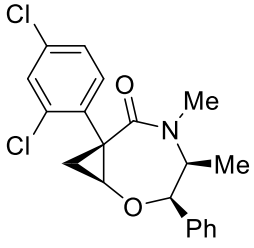
(–)-(1S,3S,4S,7S)-4,5-Dimethyl-7-(naphthalen-1-yl)-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (207d). This compound was synthesized according to typical procedure from 1-(naphthalen-1-yl)cycloprop-2-ene-1-carboxylic acid (**196d**) (200 mg, 0.95 mmol, 1.0 equiv.), and (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride (**214**) (288 mg, 1.43 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-N-methyl-1-(naphthalen-1-yl)cycloprop-2-ene-1-carboxamide (**206d**) was used at the cyclization step as is without additional purification. To this end, amide **206d** (20 mg, 0.056 mmol) was treated with powdered KOH (6.3 mg, 0.112 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.30, mp 217-220 °C). Yield 16.2 mg (0.045 mmol, 81%). $[\alpha]_D^{20}$ –115.1 (c = 0.70, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 9.30 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.86–7.80 (m, 2H), 7.72 (dd, *J* = 7.1, 1.1 Hz, 1H), 7.67–7.61 (m, 3H), 7.57–7.44 (m, 5H), 5.55 (dq, *J* = 10.8, 7.0 Hz, 1H), 4.48 (d, *J* = 10.8 Hz, 1H), 3.96 (dd, *J* = 6.3, 2.8 Hz, 1H), 2.95 (s, 3H), 1.84 (dd, *J* = 6.3, 2.8 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 137.3, 134.7, 134.6, 133.6, 129.4 (+, 2C), 129.1 (+), 128.9 (+), 128.5 (+, 2C), 128.2 (+), 127.6 (+), 126.5 (+), 126.5 (+), 125.4 (+), 124.9 (+), 80.0 (+), 52.4 (+), 51.0 (+), 34.1, 27.9 (+), 21.6 (–), 15.3 (+). FTIR (NaCl, cm^{-1}): 3003, 2918, 1645, 1454, 1391, 1329, 1233, 1152, 1088, 999, 781, 758, 700. HRMS (TOF ES): found 380.1638, calculated for $C_{24}H_{23}NO_2Na$ (M + Na) 380.1626 (3.2 ppm).



(+)-(1R,3R,4R,7R)-4,5-Dimethyl-7-(naphthalen-1-yl)-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one *(ent-***207d***)*. This compound was synthesized according to typical procedure from 1-(naphthalen-1-yl)cycloprop-2-ene-1-carboxylic acid (**196d**) (200 mg, 0.95 mmol, 1.0 equiv.), and (1*R*,2*R*)-(–)-pseudoephedrine hydrochloride (*ent*-**214**) (288 mg, 1.43 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-1-(naphthalen-1-yl)cycloprop-2-ene-1-carboxamide (*ent*-**206d**) was used at the cyclization step as is without additional purification. To this end, amide *ent*-**206d** (20 mg, 0.056 mmol) was treated with powdered KOH (6.3 mg, 0.112 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.30, mp 222-224 °C). Yield 16.8 mg (0.047 mmol, 84%). $[\alpha]_D^{20}$ +118.5 (c = 0.70, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 9.30 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.87–7.78 (m, 2H), 7.72 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.69–7.60 (m, 3H), 7.58–7.44 (m, 5H), 5.55 (dq, *J* = 10.9, 7.0 Hz, 1H), 4.48 (d, *J* = 10.8 Hz, 1H), 3.96 (dd, *J* = 6.3, 2.8 Hz, 1H), 2.95 (s, 3H), 1.84 (dd, *J* = 6.2, 2.8 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 137.3, 134.7, 134.6, 133.6, 129.4 (+, 2C), 129.1 (+), 128.9 (+), 128.5 (+, 2C), 128.2 (+), 127.6 (+), 126.5 (+), 126.5 (+), 125.4 (+), 124.9 (+), 80.0 (+), 52.4 (+), 51.0 (+), 34.1, 27.9 (+), 21.6 (–), 15.3 (+). FTIR (NaCl, cm^{-1}): 3003, 2918, 1645, 1454, 1392, 1329, 1232, 1151, 1087, 999, 781, 758, 700. HRMS (TOF ES): found 380.1608, calculated for $C_{24}H_{23}NO_2Na$ (M + Na) 380.1624 (4.7 ppm).



(+)-(1S,3R,4S,7S)-4,5-Dimethyl-3,7-diphenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (**210a**). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**196a**) (200 mg, 1.25 mmol, 1.0 equiv.), and (1*R*,2*S*)-(–)-ephedrine hydrochloride (**215**) (378 mg, 1.88 mmol, 1.5 equiv.). After extraction and filtration through a silica plug crude *N*-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-1-phenylcycloprop-2-ene-1-carboxamide (**209a**) was used at the cyclization step as is without additional purification. To this end, amide **209a.** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:2) as a colorless glass (R_f 0.28). $[\alpha]_D^{20}$ +77.0 (c = 0.70, $CHCl_3$). Yield 16.8 mg (0.055 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5H), 7.27–7.19 (m, 3H), 7.08–7.03 (m, 2H), 4.64 (qd, *J* = 7.2, 4.2 Hz, 1H), 4.51 (d, *J* = 4.3 Hz, 1H), 3.62 (dd, *J* = 6.2, 3.4 Hz, 1H), 2.70 (s, 3H), 1.89 (dd, *J* = 7.0, 3.4 Hz, 1H), 1.62 (t, *J* = 6.6 Hz, 1H), 1.08 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 138.2, 136.5, 129.0 (+, 2C), 128.6 (+), 128.2 (+, 2C), 127.8 (+, 2C), 126.8 (+), 124.6 (+, 2C), 81.2 (+), 59.4 (+), 52.3 (+), 35.1, 29.0 (+), 22.6 (–), 14.6 (+). FTIR (NaCl, cm^{-1}): 2999, 2923, 1648, 1497, 1454, 1435, 1397, 1170, 1053, 1020, 756, 713, 700. HRMS (TOF ES): found 330.1484, calculated for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470 (4.2 ppm).



(+)-(1S,3R,4S,7S)-7-(2,4-Dichlorophenyl)-4,5-dimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (210c). This compound was synthesized according to typical procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**196c**) (150 mg, 0.65 mmol, 1.0 equiv.), and (1*R*,2*S*)-(–)-ephedrine (**215**) (198 mg, 0.98 mmol, 1.5 equiv.). After

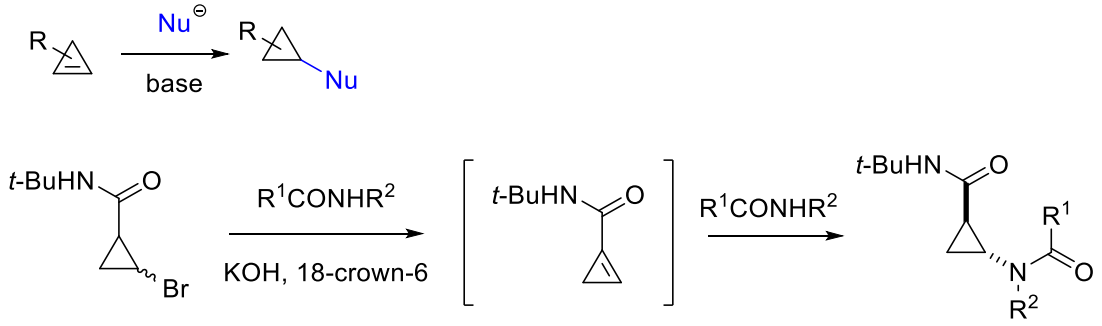
extraction and filtration through a silica plug crude 1-(2,4-dichlorophenyl)-*N*-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-N-methylcycloprop-2-ene-1-carboxamide (**209c**) was used at the cyclization step as is without additional purification. To this end, amide **209c** (60 mg, 0.16 mmol) was treated with powdered KOH (18 mg, 0.32 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.26, mp 152-157 °C). Yield 52.2 mg (0.139 mmol, 87%). $[\alpha]_D^{20}$ +27.9 (c = 0.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.7 (d, *J* = 8.5 Hz, 1H), 7.4 (d, *J* = 2.3 Hz, 1H), 7.3–7.3 (m, 3H), 7.3–7.2 (m, 3H), 5.4–5.3 (m, 1H), 4.7 (d, *J* = 4.4 Hz, 1H), 4.3 (dd, *J* = 6.2, 3.1 Hz, 1H), 2.6 (s, 3H), 1.8 (dd, *J* = 6.6, 3.1 Hz, 1H), 1.5 (t, *J* = 6.4 Hz, 1H), 1.1 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 136.8, 133.9, 133.9, 133.9 (+), 133.9, 130.7 (+), 128.6 (+), 128.3 (+, 2C), 127.7 (+, 2C), 127.7 (+), 81.1 (+), 56.6 (+), 51.4 (+), 34.4, 29.5 (+), 22.9 (–), 14.3 (+). FTIR (NaCl, cm^{-1}): 2918, 2848, 1647, 1474, 1397, 1389, 1354, 1167, 1107, 1026, 826, 756, 706. HRMS (TOF ES): found 398.0676, calculated for $C_{20}H_{19}Cl_2NO_2Na$ (M + Na) 398.0691 (3.8 ppm). The relative and absolute configuration of compound **210c** was unambiguously confirmed by single-crystal X-ray crystallography (CCDC # 1823181).

Chapter 5. Intramolecular nucleophilic addition of tethered carbamates to cyclopropenes

5.1 Introduction

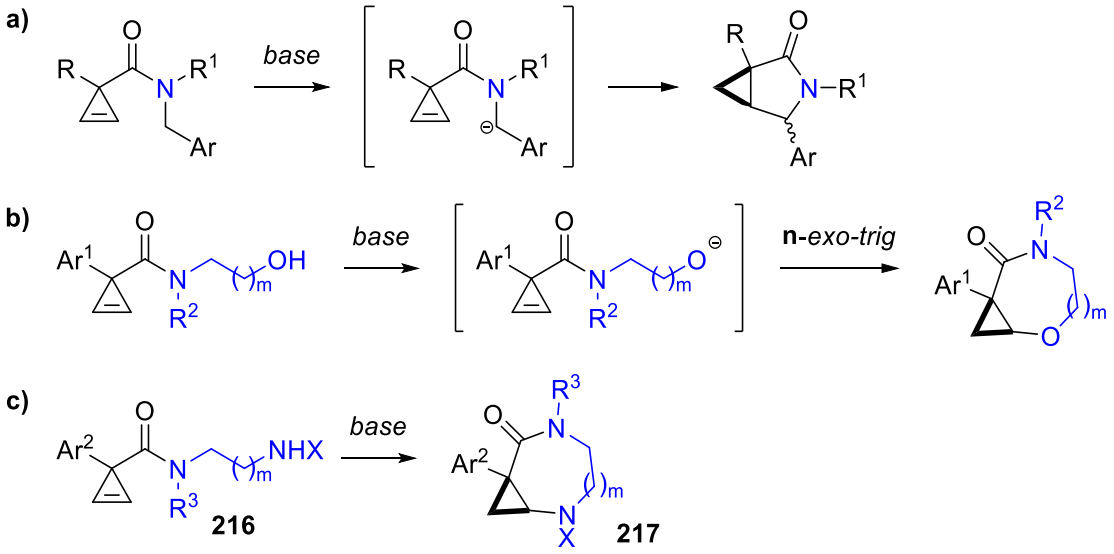
Employment of carbon-,[125,117,142] nitrogen-,[107,114,120] oxygen-,[111,114,119] sulfur-,[121] or halogen-based[122] nucleophiles has been demonstrated in the intermolecular mode of the ring-retentive addition (Scheme 66). The intramolecular version of this reaction involving nucleophilic species tethered to cyclopropenes and leading to the formation of fused bicyclic ring systems is much more challenging.

Scheme 66



We recently developed methods for transition metal-free intramolecular addition of tethered nucleophiles (Scheme 67a and Scheme 67b), employing carbon- and oxygen-based species (Chapter 3 and Chapter 4 respectively). During these studies, the resulting novel cyclopropene-fused scaffolds were identified as attractive biologically active probes possessing promising biological activity,[3] which justified further synthetic efforts, especially towards medium sized cyclic amines **217**, that could mimic β- or γ-turns of polypeptides.

Scheme 67



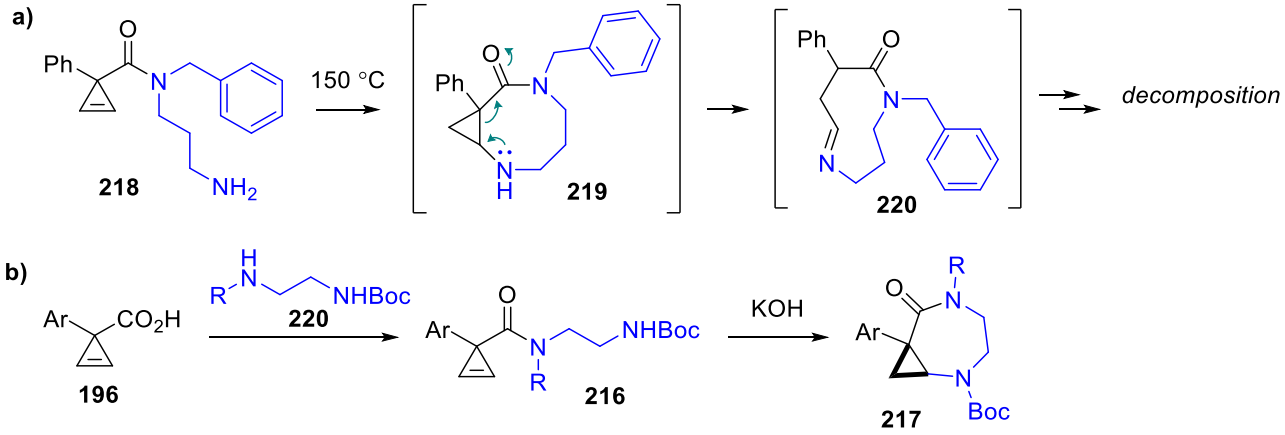
At first glance, using amine-based nucleophilic entities in intermolecular cyclizations (Scheme 67c) seemed to be a reasonably straightforward extension of the work previously performed with tethered alcohols (Scheme 67b). Unfortunately, decreased nucleophilicity of amines compared to alkoxides, paired with lowered acidity of amines compared to alcohols complicated the development of direct base assisted addition of tethered amines to cyclopropanes.

5.2 Intramolecular addition of tethered nitrogen-based nucleophiles to cyclopropenes

It should be noted that for successful base-assisted addition of the heteroatom-based entities across C=C bond of cyclopropenes, a fine balance between nucleophilicity and acidity must be maintained.[107,111,114,143] Thus, the ring-retentive reaction of cyclopropenes with primary amines (**9**, NHX = NH_2, NHAlk in Scheme 67c) cannot be achieved since the nucleophilicity of these neutral amines is much lower that of alkoxides, and their acidity is not sufficient to produce much more reactive anionic entities in the presence of typically employed weak bases. Increasing the

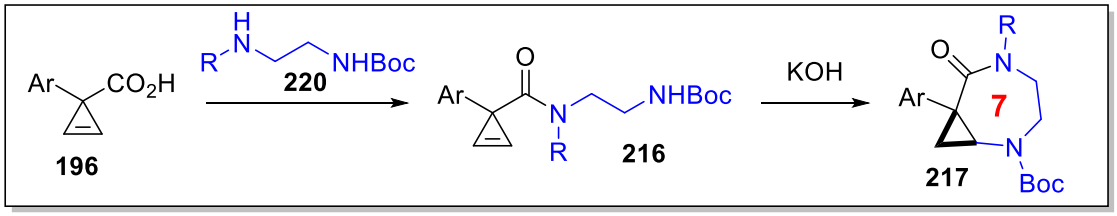
strength of the base proved counterproductive, since concurrent deprotonation of acidic C-H bonds of cyclopropene occurs, greatly diminishing it's electrophilicity. At higher temperature it was possible to force a thermally-induced intramolecular nucleophilic attack in substrate **218**, but the resulting donor-acceptor cyclopropane **219** tended towards facile ring-cleavage [144, 145] and subsequent decomposition of cyclic imine **220** (Scheme 68a, also see Chapter 2).

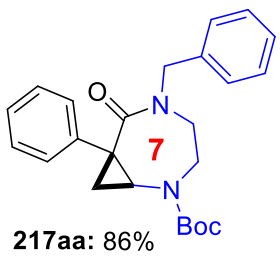
Scheme 68



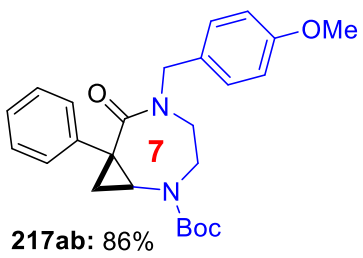
Arguably, the best solution to this problem would be the employment of an appropriate protecting group at the amine function, acidifying the N-H bond in the precursor and moderating the electron-donating character of the nitrogen atom in the cyclic product. Given the availability of the corresponding starting materials we focused our initial investigation on reactivity of Boc-protected amines **216** (Scheme 68b). To this end, 1-phenylcycloprop-2-ene-1-carboxylic acid **196a** (Scheme 69) was subjected to the acylation reaction with *tert*-butyl (2-aminoethyl)carbamate **220a**. Without purification, the resulting amide **216aa** was treated with powdered KOH to afford the desired 2,5-diazabicyclo[5.1.0]octan-6-one **217aa** as the sole product in 86% overall yield.

Scheme 69

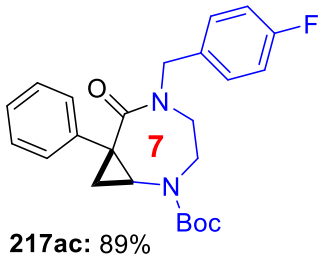




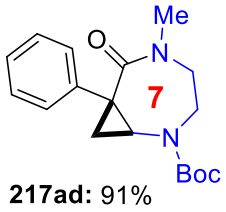
217aa: 86%



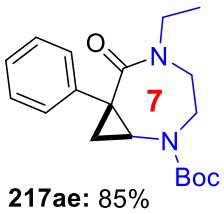
217ab: 86%



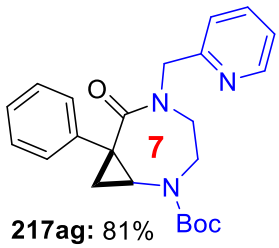
217ac: 89%



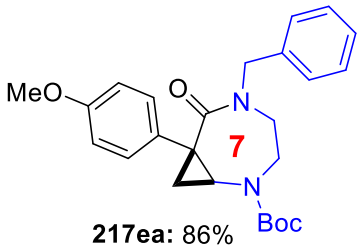
217ad: 91%



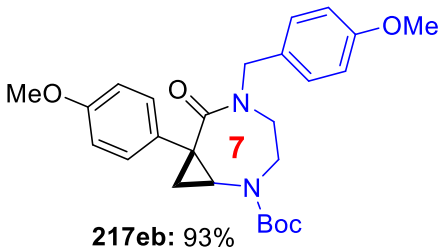
217ae: 85%



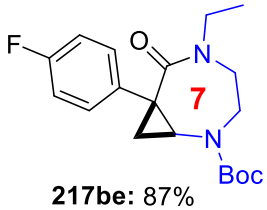
217ag: 81%



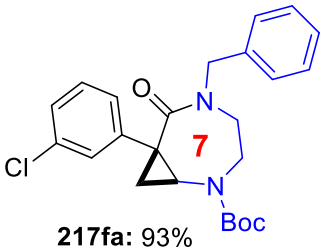
217ea: 86%



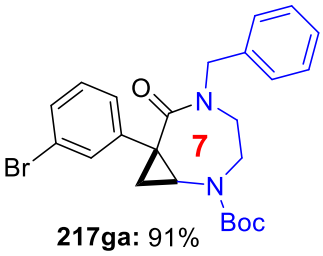
217eb: 93%



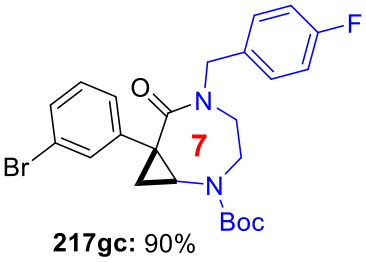
217be: 87%



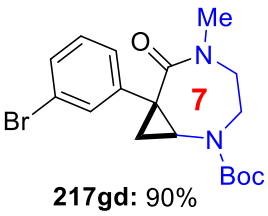
217fa: 93%



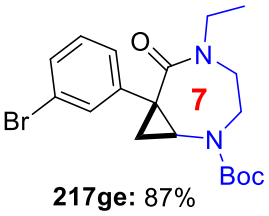
217ga: 91%



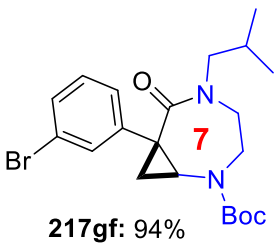
217gc: 90%



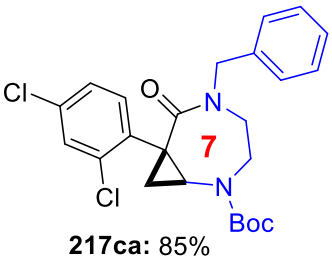
217gd: 90%



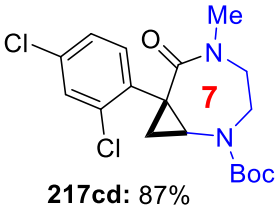
217ge: 87%



217gf: 94%



217ca: 85%



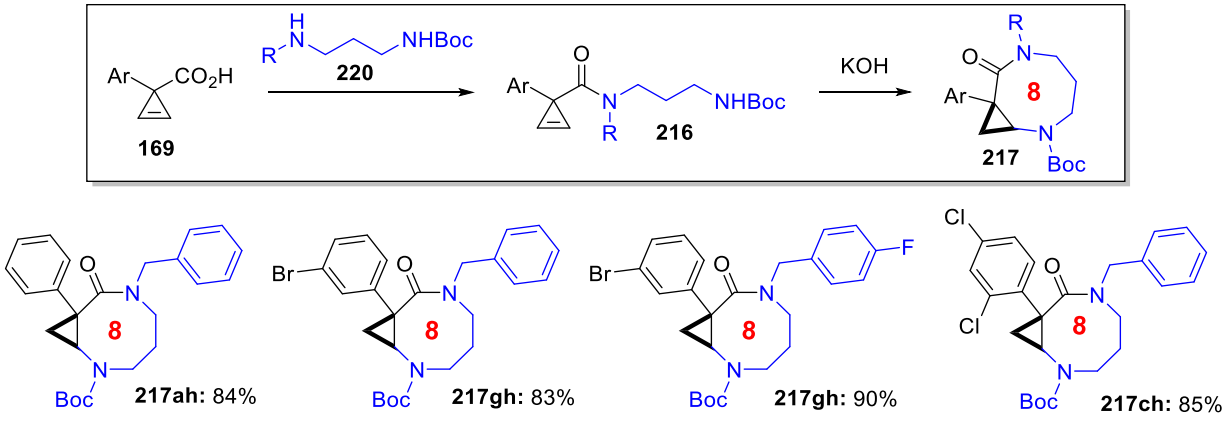
217cd: 87%

This reaction proved to be pretty general for *7-exo-trig* cyclization showing high tolerance for

substituents at the amide nitrogen and at the quaternary carbon of cyclopropene. It was shown that the starting amines could be protected not only by benzyl or substituted benzyl groups, but also by alkyl (**220d-f**) or 2-picolyl moieties (**220g**). The aryl group at the quaternary center of cyclopropene can bear alkoxy- (**196e**), or halogen substituents (**196b,c,f,g**). All seven-membered bicyclic amides were obtained in very high yields as sole products (Scheme 69).

Similarly, acylation of cyclopropene-3-carboxylic acids **196** with *N*-benzylated derivatives of (3-aminopropyl)carbamate **220h-j** afforded the corresponding tethered carbamates **216** in crude form (Scheme 70). After treatment with a base, the latter underwent smooth 8-*exo*-*trig* cyclization leading to the formation of 2,6-diazabicyclo[6.1.0]nonan-7-ones **217**.

Scheme 70



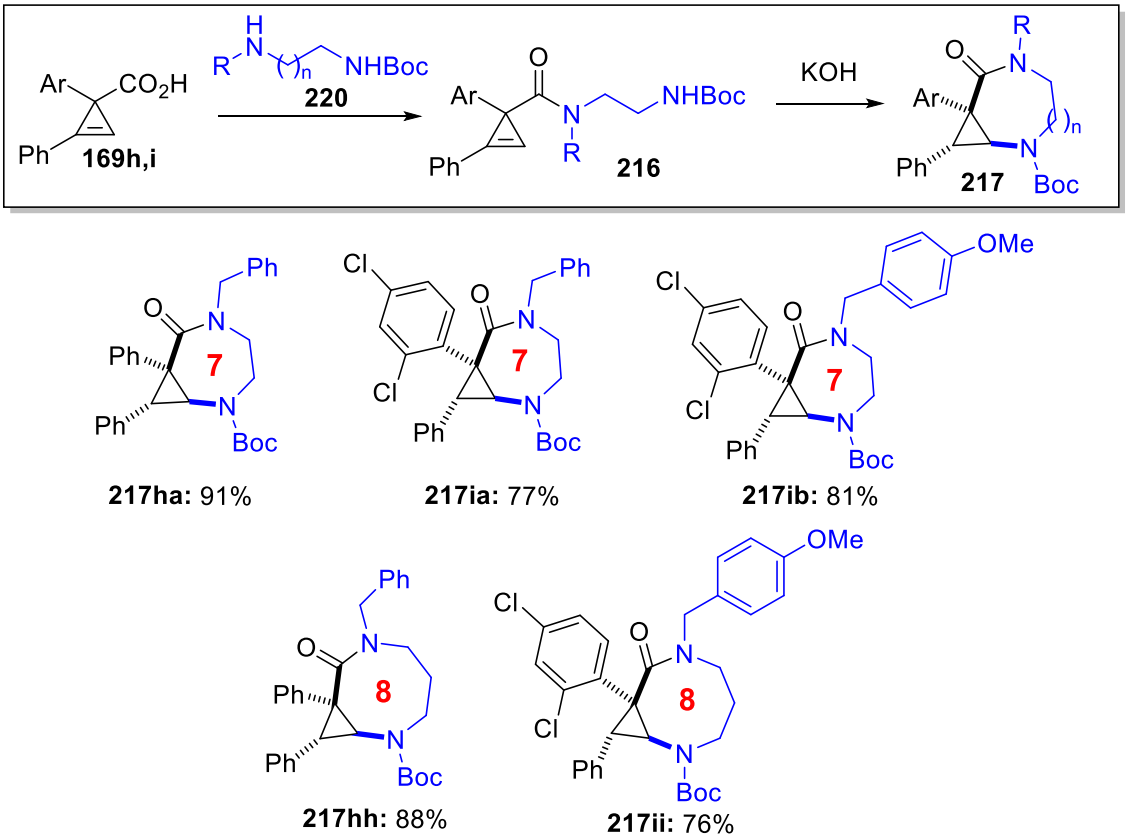
5.3 Diastereoselectivity of the intermolecular addition of nitrogen-based nucleophiles to cyclopropenes

With positive initial result in hand we studied the effect of additional stereogenic centers on the diastereoselectivity of this reaction.

First, we employed chiral cycloprop-2-enecarboxylic acids **169h,i** (in racemic form, Scheme 71). Ethanolamines and propanolamines were converted into mono-carbamates **220** uneventfully,

and the following condensation afforded tertiary amide species **216**, possessing chiral cyclopropene units (Scheme 71). We were pleased to find, that the reaction of these precursors proceeded regio- and diastereoselectively, affording in high yields seven- (**217ha, 217ia, 217ib**) and eight-membered (**217hh, 217ii**) heterocycles as sole products with relative configurations (1*S**,7*S**,8*R**) and (1*S**,8*S**,9*R**), respectively. Overall, the addition of the N-H moiety across the C=C bond of cyclopropene proceeded in a formal *syn*-fashion.

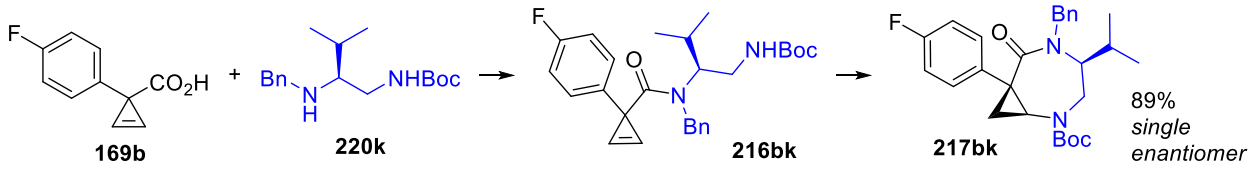
Scheme 71



Next, the reaction of tethered carbamate **216bk** assembled by acylation of *L*-valine-derived chiral amine **220k** with prochiral cycloprop-2-enecarboxylic acid **169b** was evaluated (Scheme 72). The cyclopropene moiety in **216bk** possesses two diastereotopic sites for nucleophilic attack,

but only one of them is being involved in the reaction giving rise to product **217bk** with (1*S*,4*S*,7*S*)-configuration and bulky isopropyl group in the more favored bowsprit configuration (as shown by X-ray crystallography, CCDC #1854746). This stereochemical outcome is very similar to the one recently reported for assembly of cyclopropane-fused oxazepanones (Chapter 4.3) via 7-*exo-trig* cyclizations of tethered chiral alkoxides.

Scheme 72



5.4 Preliminary evaluation of biological activity

The obtained structures constitute very attractive biological probes as this unique heterocyclic scaffold just recently emerged on the chemical space map (Chapter 1.3).[3] Accordingly, a preliminary biological evaluation of a few representative compounds for anticancer activity using HeLa cell line (ATCC CCL-2) as a model for human cervical adenocarcinoma, through the measurements of mitochondrial dehydrogenase activities using the MTT method[137] was performed by the group of Prof. Frolova.[4] Preliminary tests revealed that some of the compounds possess promising anticancer activity, and the level of biological activity is very dependent on the character of substituents in designed structures (Figure 15). For example, the changing of the substituent on amide nitrogen from aryl or benzyl groups to alkyl group eliminates the antiproliferative activity of synthesized compounds **8** completely. The same effect was observed as a result of the replacement of H with Ph at the CH_2-group of the cyclopropane ring. At the same time, significant improvement of biological activity (almost three-fold) was achieved after incorporation of Br in

the *meta*-position of the aryl ring at quaternary cyclopropane carbon. Thus, the obtained compounds **217gc**, **217gj** revealed great promise as novel anticancer scaffolds and will be a subject of further investigations.

See section A2 of Appendix for experimental data.

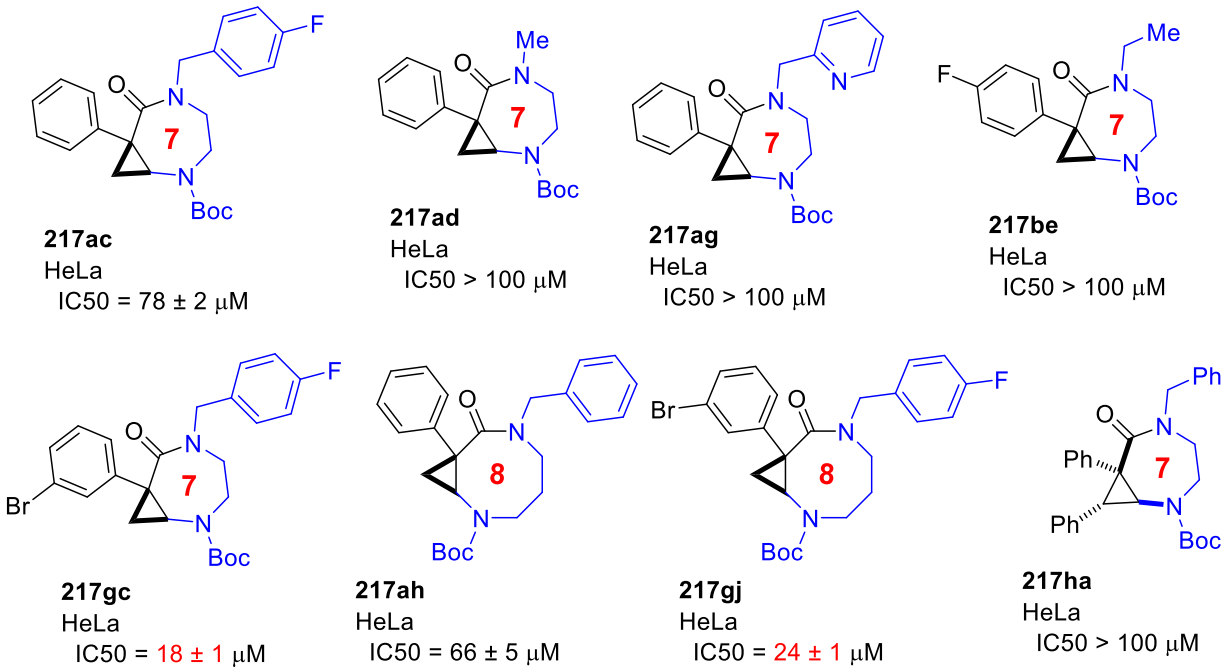


Figure 15. Biological activity of selected 2,5-diazabicyclo[5.1.0]octan-6-ones and 2,6-diazabicyclo[6.1.0]nonan-7-ones

5.5 Conclusion

A novel and highly efficient strain-release-driven cyclization involving potassium-templated ring-retentive 7- and 8-*exo*-*trig* nucleophilic attack of tethered nitrogen-based nucleophiles (Boc-protected amines) at cyclopropene double bond was demonstrated. The described reaction proceeds in highly regio- and diastereoselective fashion and provides expedited access to previously unknown 2,5-diazabicyclo[5.1.0]octan-6-ones and 2,6-diazabicyclo[6.1.0]nonan-7-ones as sole products in high yields. Utilization of chiral diamines derived from natural aminoacids

allows to obtain cyclopropane-fused medium-sized nitrogen-based heterocycles in enantiomerically pure form. Preliminary evaluation of bioactivity of these previously unknown drug-like scaffold was performed to reveal several structures with promising anti-cancer properties.

5.6 Experimental

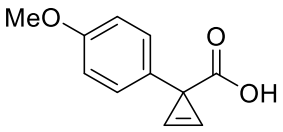
5.6.1 General information

NMR spectra were recorded on a Bruker Avance DRX500 (500 MHz) with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were registered with broadband decoupling. The (+) and (−) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. IR spectra were recorded on a ThermoFisher Nicolet iS 5 FT-IR Spectrometer. HRMS was carried out on LCT Premier (Micromass Technologies) instrument employing ESI TOF detection techniques. Glassware used in moisture-free syntheses was flame-dried in vacuum prior to use. Column chromatography was carried out on silica gel (Sorbent Technologies, 40−63 mm). Silica gel plates (Sorbent Technologies Silica XG 200 mm) were used for TLC analyses. Anhydrous dichloromethane was obtained by passing degassed commercially available HPLC-grade inhibitor-free solvent consecutively through two columns filled with activated alumina and stored over molecular sieves under nitrogen. Water was purified by dual stage deionization followed by dual stage reverse osmosis. Anhydrous THF was obtained by refluxing commercially available solvent over calcium hydride followed by distillation in a stream of dry nitrogen. All other reagents and solvents were purchased from commercial vendors and used as received.

5.6.2 Biological Studies: Materials and Methods

Biological Studies. Cell culture: HeLa cells were cultured in DMEM supplemented with 10% FBS. To evaluate antiproliferative properties of the synthesized compounds, the cells were trypsinized and seeded $4 \cdot 10^3$ cells per well into 96-well microtiter plates. The cells were grown for 24 h before treatment. MTT assay for HeLa: All compounds were dissolved in DMSO at a concentration of either 100 or 50 mM prior to cell treatment. The cells were treated at concentrations ranging from 0.004 to 100 μM and incubated for 48 h in 200 μL of media. Twenty microliters of MTT reagent in serum-free medium (5 mg/mL) was added to each well and incubated further for 2 h. Media was removed, and the resulting formazan crystals were resolubilized in 100 μL of DMSO. A490 was measured using a Thermomax Molecular Device plate reader. The experiments were performed in quadruplicate and repeated at least twice for each compound per cell line. Cells treated with 0.1% DMSO were used as a negative control, and phenyl arsine oxide (PAO) was used as a positive killing control.

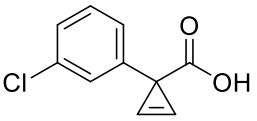
5.6.3 Synthesis of Starting Materials



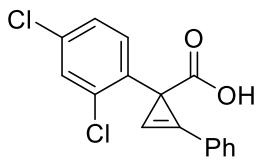
1-(4-Methoxyphenyl)cycloprop-2-ene-1-carboxylic acid **(169e)**. Typical procedure: Methyl (4-methoxyphenyl)acetate (6.86 g, 41.3 mmol, 1.00 equiv.) and tosyl azide (9.0 g, 45.4 mmol, 1.1 equiv.) were stirred in acetonitrile (150 mL) at 0 °C, and DBU (7.54 g, 49.5 mmol, 1.2 equiv.) was added dropwise. Upon complete addition the reaction was allowed to warm to room temperature and was stirred overnight. The solvent was then evaporated and the residue was partitioned between saturated ammonium chloride and methylene chloride. The aqueous phase was then extracted with methylene chloride (3 × 30 mL). Combined organic phases were then washed with brine, dried with MgSO4, filtered, and

concentrated. The recovered material was then mixed with Silica gel (15 g) and filtered through a short pad of Silica gel using hexanes. Crude methyl 2-diazo-2-(4-methoxyphenyl)acetate was obtained as a red oil. This material was then mixed with trimethylsilylacetylene (2 mL), and added via a syringe pump over 18 h to a stirring and refluxing suspension of rhodium(II) acetate dimer (27.4 mg, 0.124 mmol, 0.3 mol%) in trimethylsilylacetylene (47 mL, 413 mmol, 10.0 equiv.). After complete addition, the reaction was monitored by gas chromatography until complete consumption of the starting material was observed. Once this was achieved, the reflux condenser was replaced with a distillation head and most of the trimethylsilylacetylene was recovered by distillation at ambient pressure. The residual solvent was then removed under vacuum. The reaction mixture was then purified by short column chromatography eluting with a mixture of hexane : EtOAc (10 : 1). Crude ethyl 1-(4-methoxyphenyl)-2-(trimethylsilyl)cycloprop-2-ene-1-carboxylate was obtained as a yellowish oil, which was stirred at 0 °C in a mixture of methanol and THF (1 : 1, 200 mL). An aqueous solution of sodium hydroxide (2 M, 200 mL) was added dropwise and the mixture was stirred for 18 h. Organic solvents were then removed under vacuum and the remaining aqueous solution was washed with dichloromethane (3 × 50 mL). The mixture was acidified to pH 2 with 2 M aqueous HCl and extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The obtained product was purified by column chromatography on silica gel eluting with a mixture of hexane/EtOAc (2 : 1). The title compound was obtained as an off-white crystalline solid (Rf 0.3, mp 115–116 °C). Overall yield 2.198 g (11.6 mmol, 28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 2H), 7.24–7.19 (m, 2H), 6.87–6.81 (m, 2H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.7, 158.5, 132.9, 129.5 (+, 2C), 113.8 (+, 2C), 107.6 (+, 2C), 55.4 (+), 29.7.

FT IR (NaCl, cm^{-1}): 3440 (br.), 1689, 1659, 1514, 1246, 1030, 773. HRMS (TOF ES): found 189.0551, calculated for $C_{11}H_9O_3$ $(M - H)^-$ 189.0552 (0.5 ppm).

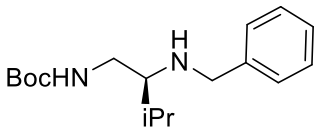


1-(3-Chlorophenyl)cycloprop-2-ene-1-carboxylic acid **(169f)**. This compound was obtained from methyl (3-chlorophenyl)acetate (5.65 g, 33.1 mmol) using the protocol described for the synthesis of 1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxylic acid (*vide supra*). The title compound was obtained as an off-white crystalline solid (mp 84–86 °C). Yield 4.71 g (24.2 mmol, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (td, *J* = 1.8, 0.6 Hz, 1H), 7.24–7.22 (m, 1H), 7.21 (t, *J* = 1.9 Hz, 1H), 7.20 (s, 2H), 7.19–7.17 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.9, 142.7, 134.1, 129.5 (+), 128.7 (+), 127.1 (+), 126.7 (+), 106.8 (+, 2C), 30.0. FT IR (NaCl, cm^{-1}): 3160 (br.), 1690, 1674, 1595, 1413, 1269, 1091, 984. HRMS (TOF ES): found 193.0057, calculated for $C_{10}H_6ClO_2$ $(M - H)^-$ 193.0056 (0.5 ppm).

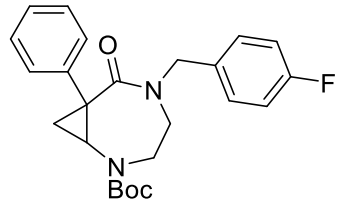


1-(2,4-Dichlorophenyl)-2-phenylcycloprop-2-ene-1-carboxylic acid **(169i)**. This compound was obtained using methyl (2,4-dichlorophenyl)acetate (2.11 g, 10.3 mmol) and a solution of ethynylbenzene (3.15 g, 30.9 mmol, 3.0 equiv.) in 20 mL of CH_2Cl_2 according to the protocol described for the synthesis of 1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxylic acid (*vide supra*). The title compound was obtained as a light-beige crystalline solid (mp 153–154 °C). Yield 1.79 g (5.87 mmol, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.68 (m, 2H), 7.50–7.42 (m, 3H), 7.37 (d, *J* = 2.1 Hz, 1H), 7.31 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.11 (dd, *J* = 8.2, 2.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.0, 137.9, 135.9, 133.9, 131.1 (+), 130.6 (+), 130.1 (+, 2C), 129.5 (+), 129.2 (+, 2C), 127.3 (+), 125.2, 118.1,

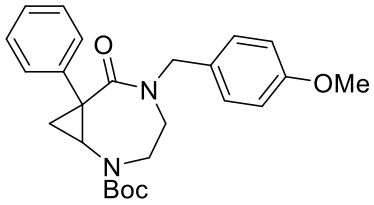
101.3 (+), 32.8. FT IR (NaCl, cm^{-1}): 3381 (br.), 1685, 1471, 1260,1101, 821, 698. HRMS (TOF ES): found 302.9982, calculated for $C_{16}H_9Cl_2O_2$ $(M - H)^-$ 302.9980 (0.7 ppm).



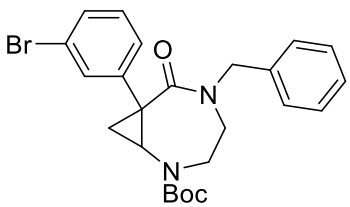
tert-Butyl (S)-(2-(benzylamino)-3-methylbutyl)carbamate (**220k**). A 15 mL autoclave vessel was charged with *tert*-butyl (*S*)-(2-amino-3-methylbutyl)carbamate (300 mg, 1.48 mmol, 1.0 equiv.), benzaldehyde (182 μL, 189 mg, 1.78 mmol, 1.2 equiv.), 10 wt% palladium on carbon (78.9 mg, 0.074 mmol, 0.05 equiv.), and methanol (3 mL). The mixture was stirred under hydrogen gas (1.5 atm.) overnight. The catalyst was removed by vacuum filtration through Celite® 545 non-acid-washed filter aid washing with methanol, then the resulting mixture was evaporated. The product was isolated by column chromatography eluting with a chloroform/methanol mixture (40:1) as a colorless oil (R_f 0.24). Yield: 239 mg (0.82 mmol, 55%). $[\alpha]_D^{20}$ +1.8 (c = 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.15 (m, 5H), 4.97 (br. s, 1H), 3.70 (s, 2H), 3.29–3.12 (m, 1H), 2.96 (dt, *J* = 12.9, 6.2 Hz, 1H), 2.36 (q, *J* = 6.2 Hz, 1H), 1.76 (nonet, *J* = 6.8 Hz, 1H), 1.38 (s, 9H), 0.86 (dd, *J* = 17.1, 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 140.6, 128.5 (+, 2C), 128.2 (+, 2C), 127.0 (+), 79.0, 62.1 (+), 51.5 (–), 40.5 (–), 28.5 (+, 3C), 19.2 (+, 2C), 18.4 (+). FTIR (NaCl, cm^{-1}): 3350 (br.), 2963, 1699,1495, 1366, 1171738, 699. HRMS (TOF ES): found 293.222, calculated for $C_{17}H_{29}N_2O_2$ (M + H) 293.229 (2.4 ppm).



tert-Butyl 5-(4-fluorobenzyl)-6-oxo-7-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ac). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**169a**) (200 mg, 1.25 mmol, 1.0 equiv.), and *tert*-butyl (2-((4-fluorobenzyl)amino)ethyl)carbamate (402 mg, 1.5 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-(4-fluorobenzyl)-1-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ac**) was used at the cyclization step as is without additional purification. To this end, amide **216ac** (60 mg, 0.146 mmol) was treated with powdered KOH (20.5 mg, 0.365 mmol). The reaction mixture was vigorously stirred at 35 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.26, mp 112-113 ºC). Yield: 53.3 mg (0.13 mmol, 89%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.14 (d, *J* = 7.4 Hz, 2H), 7.09 (dd, *J* = 8.5, 6.7 Hz, 2H), 7.05–7.00 (m, 1H), 6.93 (dd, *J* = 8.4, 5.5 Hz, 2H), 6.75 (t, *J* = 8.7 Hz, 2H), 4.34 (br.s, 1H), 4.20 (br.s, 1H), 3.51 (br.s, 1H), 3.37 (td, *J* = 13.2, 4.1 Hz, 1H), 2.47 (dd, *J* = 7.1, 4.6 Hz, 1H), 2.44–2.37 (m, 2H), 1.95 (t, *J* = 5.6 Hz, 1H), 1.50 (t, *J* = 6.9 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.9, 162.8 (d, *J* = 245.3 Hz), 156.5, 139.2, 134.2 (d, *J* = 3.5 Hz), 130.1 (d, *J* = 8.1 Hz, +, 2C), 129.0 (+, 2C), 127.1 (+), 125.8 (+, 2C), 115.6 (d, *J* = 21.3 Hz, +, 2C), 80.0, 48.9 (–), 44.5 (–), 43.5 (–), 37.3 (+), 36.3, 28.4 (+, 3C), 26.4 (–). FTIR (NaCl, cm^{-1}): 2976, 2929, 1701, 1650, 1509, 1365, 1346, 1222, 1146, 853, 765, 697. HRMS (TOF ES): found 433.1910, calculated for $C_{24}H_{27}FN_2O_3Na$ (M + Na) 433.1903 (1.6 ppm).

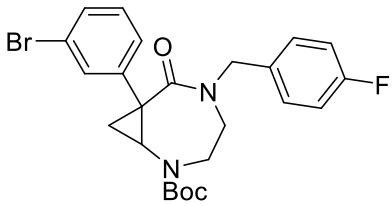


tert-Butyl 5-(4-methoxybenzyl)-6-oxo-7-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ab). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**169a**) (200 mg, 1.25 mmol, 1.0 equiv.), and *tert*-butyl (2-((4-methoxybenzyl)amino)ethyl)carbamate (420 mg, 1.5 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-(4-methoxybenzyl)-1-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ab**) was used at the cyclization step as is without additional purification. To this end, amide **216ab** (60 mg, 0.142 mmol) was treated with powdered KOH (19.9 mg, 0.355 mmol). The reaction mixture was vigorously stirred at 35 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.25, mp 134-136 ^{o}C). Yield: 51.7 mg (0.122 mmol, 86%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.21–7.17 (m, 2H), 7.11 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.09–7.05 (m, 2H), 7.05–6.99 (m, 1H), 6.76–6.69 (m, 2H), 4.50 (br.s, 1H), 4.31 (br.s, 1H), 3.58 (br.s, 1H), 3.41 (td, *J* = 13.3, 4.1 Hz, 1H), 3.32 (s, 3H), 2.59–2.51 (m, 1H), 2.48 (dd, *J* = 7.1, 4.7 Hz, 1H), 2.43 (dd, *J* = 12.8, 3.9 Hz, 1H), 1.99 (t, *J* = 5.6 Hz, 1H), 1.53 (t, *J* = 6.8 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.8, 159.8, 156.5, 139.5, 130.4, 129.8 (+, 2C), 129.0(+, 2C), 127.0 (+), 125.8 (+, 2C), 114.5 (+, 2C), 79.9, 54.8 (+), 49.1 (–), 44.6 (–), 43.3 (–), 37.5 (+), 36.4, 28.4 (+, 3C), 26.4 (–). FTIR (NaCl, cm^{-1}): 2974, 2923, 1701, 1651, 1513, 1393, 1248, 1146, 1032, 808, 760. HRMS (TOF ES): found 445.2104, calculated for $C_{25}H_{30}N_2O_4Na$ (M + Na) 445.2103 (0.2 ppm).



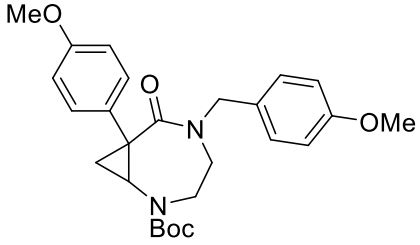
tert-Butyl 5-benzyl-7-(3-bromophenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ga). This compound was synthesized according to Typical Procedure from 1-(3-

bromophenyl)cycloprop-2-ene-1-carboxylic acid (**169g**) (200 mg, 0.84 mmol, 1.0 equiv.), and *tert*-butyl (2-(benzylamino)ethyl)carbamate (251 mg, 1 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-benzyl-1-(3-bromophenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ga**) was used at the cyclization step as is without additional purification. To this end, amide **216ga** (60 mg, 0.127 mmol) was treated with powdered KOH (17.9 mg, 0.319 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless solid (R_f 0.4, mp 151-152 ºC). Yield: 54.6 mg (0.116 mmol, 91%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.38 (t, *J* = 1.9 Hz, 1H), 7.19–7.13 (m, 2H), 7.13–7.01 (m, 5H), 6.73 (t, *J* = 7.9 Hz, 1H), 4.51 (br.s, 1H), 4.16 (br.s, 1H), 3.51 (br.s, 1H), 3.20 (td, *J* = 13.4, 4.1 Hz, 1H), 2.48–2.37 (m, 1H), 2.33 (dd, *J* = 12.9, 4.0 Hz, 1H), 2.29 (dd, *J* = 7.1, 4.7 Hz, 1H), 1.91 (t, *J* = 5.7 Hz, 1H), 1.41 (s, 9H), 1.39–1.35 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 156.3, 141.9, 138.2, 130.5 (+), 130.2 (+), 128.9 (+, 2C), 128.7 (+), 128.4 (+, 2C), 127.7 (+), 124.8 (+), 123.4, 80.0, 49.6 (–), 44.3 (–), 43.3 (–), 37.3 (+), 36.0, 28.4 (+, 3C), 26.6 (–). FTIR (NaCl, cm^{-1}): 2974, 2926, 1702, 1654, 1476, 1393, 1366, 1344, 1249, 1147, 1062, 994, 777, 754, 697. HRMS (TOF ES): found 493.1109, calculated for $C_{24}H_{27}BrN_2O_3Na$ (M + Na) 493.1103 (1.2 ppm).



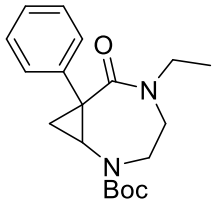
tert-Butyl 7-(3-bromophenyl)-5-(4-fluorobenzyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217gc). This compound was synthesized according to Typical Procedure from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (**169g**) (200 mg, 0.84 mmol, 1.0 equiv.), and *tert*-butyl (2-((4-fluorobenzyl)amino)ethyl)carbamate (269 mg, 1 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(1-(3-bromophenyl)-*N*-(4-

fluorobenzyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216gc**) was used at the cyclization step as is without additional purification. To this end, amide **216gc** (60 mg, 0.123 mmol) was treated with powdered KOH (17.2 mg, 0.307 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless solid (R_f 0.4, mp 156-157 °C). Yield: 54.1 mg (0.111 mmol, 90%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.35 (t, *J* = 1.9 Hz, 1H), 7.19–7.13 (m, 1H), 7.01–6.96 (m, 1H), 6.92 (dd, *J* = 8.4, 5.5 Hz, 2H), 6.80–6.71 (m, 3H), 4.31 (br. s, 1H), 4.11 (br. s, 1H), 3.46 (br. s, 1H), 3.20 (ddd, *J* = 15.4, 13.4, 4.2 Hz, 1H), 2.42–2.31 (m, 2H), 2.29 (dd, *J* = 7.1, 4.7 Hz, 1H), 1.88 (dd, *J* = 6.7, 4.7 Hz, 1H), 1.40 (s, 9H), 1.43–1.34 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 162.8 (d, *J* = 246.0 Hz), 156.3, 141.8, 134.0 (d, *J* = 3.4 Hz), 130.5 (+), 130.3 (+), 130.1 (d, *J* = 8.1 Hz, +, 2C), 128.7 (+), 124.7 (+), 123.4, 115.7 (d, *J* = 21.3 Hz, +, 2C), 80.1, 48.9 (–), 44.3 (–), 43.4 (–), 37.3 (+), 35.9, 28.4 (+, 3C), 26.5 (–). FTIR (NaCl, cm^{-1}): 2977, 2931, 1701, 1652, 1594, 1509, 1477, 1412, 1394, 1344, 1249, 1222, 1201, 1148, 1063, 994, 854, 816, 778, 736, 693. HRMS (TOF ES): found 511.1001, calculated for $C_{24}H_{26}BrFN_2O_3Na$ (M + Na) 511.1009 (1.6 ppm).



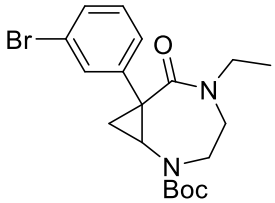
tert-Butyl 5-(4-methoxybenzyl)-7-(4-methoxyphenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217eb). This compound was synthesized according to Typical Procedure from 1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxylic acid (**169e**) (200 mg, 1.05 mmol, 1.0 equiv.), and *tert*-butyl (2-((4-methoxybenzyl)amino)ethyl)carbamate (354 mg, 1.26 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-(4-methoxybenzyl)-1-(4-

methoxyphenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216eb**) was used at the cyclization step as is without additional purification. To this end, amide **216eb** (60 mg, 0.133 mmol) was treated with powdered KOH (18.6 mg, 0.332 mmol). The reaction mixture was vigorously stirred at 35 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless glass (R_f 0.43). Yield: 55.9 mg (0.123 mmol, 93%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.19–7.16 (m, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.78–6.70 (m, 4H), 4.57 (br.s, 1H), 4.26 (br.s, 1H), 3.63 (br.s, 1H), 3.51 (td, *J* = 13.4, 3.9 Hz, 1H), 3.31 (s, 3H), 3.31 (s, 3H), 2.62–2.54 (m, 1H), 2.51–2.46 (m, 2H), 1.97 (t, *J* = 5.5 Hz, 1H), 1.51 (t, *J* = 6.8 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 170.1, 159.7, 159.3, 156.6, 131.3, 130.4, 129.7 (+, 2C), 127.3 (+, 2C), 114.7 (+, 2C), 114.5 (+, 2C), 79.8, 54.9 (+), 54.8 (+), 49.0 (–), 44.6 (–), 43.3 (–), 36.9 (+), 36.0, 28.5 (+, 3C), 26.1 (–). FTIR (NaCl, cm^{-1}): 2926, 1700, 1649, 1514, 1393, 1248, 1176, 1146, 1032, 829, 784. HRMS (TOF ES): found 475.2213, calculated for $C_{26}H_{32}N_2O_5Na$ (M + Na) 475.2209 (0.8 ppm).



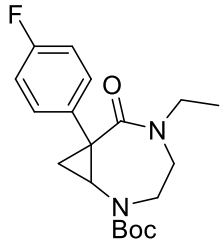
tert-Butyl 5-ethyl-6-oxo-7-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ae). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**217a**) (200 mg, 1.25 mmol, 1.0 equiv.), and *tert*-butyl (2-(ethylamino)ethyl)carbamate (282 mg, 1.5 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-ethyl-1-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ae**) was used at the cyclization step as is without additional purification. To this end, amide **216ae** (60 mg, 0.182 mmol) was treated with powdered KOH (25.5 mg, 0.455 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc

mixture (2:1) as a colorless glass (R_f 0.43). Yield: 51.1 mg (0.155 mmol, 85%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.15–7.07 (m, 4H), 7.04–6.99 (m, 1H), 3.80 (br.t, *J* = 10.8 Hz, 1H), 3.42–3.28 (m, 2H), 3.01 (dq, *J* = 14.1, 7.1 Hz, 1H), 2.56–2.48 (m, 1H), 2.46 (dd, *J* = 7.1, 4.6 Hz, 1H), 2.30 (dd, *J* = 15.2, 4.6 Hz, 1H), 1.92 (t, *J* = 5.7 Hz, 1H), 1.48 (t, *J* = 6.9 Hz, 1H), 1.41 (s, 9H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.1, 156.6, 139.6, 128.9 (+, 2C), 126.9 (+), 125.7 (+, 2C), 79.9, 45.0 (–), 43.6 (–), 41.3 (–), 37.7 (+), 36.5, 28.5 (+, 3C), 26.3 (–), 13.5 (+). FTIR (NaCl, cm^{-1}): 2973, 2926, 1699, 1652, 1429, 1366, 1346, 1175, 1146, 1065, 757, 697, 614. HRMS (TOF ES): found 353.1836, calculated for $C_{19}H_{26}N_2O_3Na$ (M + Na) 353.1841 (1.4 ppm).



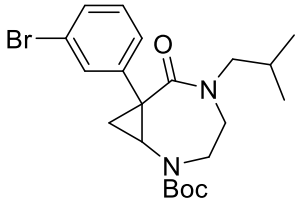
tert-Butyl 7-(3-bromophenyl)-5-ethyl-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ge). This compound was synthesized according to Typical Procedure from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (**169g**) (200 mg, 0.84 mmol, 1.0 equiv.), and *tert*-butyl (2-(ethylamino)ethyl)carbamate (190 mg, 1 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(1-(3-bromophenyl)-*N*-ethylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ge**) was used at the cyclization step as is without additional purification. To this end, amide **216ge** (60 mg, 0.147 mmol) was treated with powdered KOH (20.6 mg, 0.367 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless glass (R_f 0.4). Yield: 52.2 mg (0.128 mmol, 87%). ^{1}H NMR (400 MHz, C_6D_6) δ 7.30 (t, *J* = 1.9 Hz, 1H), 7.16–7.11 (m, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.70 (t, *J* = 7.9 Hz, 1H), 3.73 (br.s, 1H), 3.36–3.20 (m, 1H), 3.16–3.07 (m, 1H), 2.86 (br.s, 1H), 2.40 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.23 (dd, *J* = 7.2, 4.7 Hz, 1H), 2.15 (dd, *J* = 15.4, 4.5 Hz, 1H), 1.85 (br.s, 1H), 1.39 (s, 9H), 1.42–1.33 (m,

1H), 0.80 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 168.5, 156.4, 142.1, 130.5 (+), 130.1 (+), 128.5 (+), 124.9 (+), 123.3, 80.1, 44.8 (–), 43.5 (–), 41.4 (–), 37.4 (+), 36.2, 28.4 (+, 3C), 26.3, 13.4 (+). FTIR (NaCl, cm^{-1}): 2973, 2928, 1701, 1652, 1477, 1394, 1366, 1344, 1249, 1147, 856, 778, 694. HRMS (TOF ES): found 431.0953, calculated for $C_{19}H_{25}BrN_2O_3Na$ (M + Na) 431.0946 (1.6 ppm).

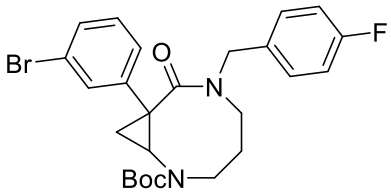


tert-Butyl 5-ethyl-7-(4-fluorophenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217be). This compound was synthesized according to Typical Procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**217b**) (200 mg, 1.12 mmol, 1.0 equiv.), and *tert*-butyl (2-(ethylamino)ethyl)carbamate (256 mg, 1.35 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-ethyl-1-(4-fluorophenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216be**) was used at the cyclization step as is without additional purification. To this end, amide **216be** (60 mg, 0.172 mmol) was treated with powdered KOH (24.2 mg, 0.431 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.45, mp 146-148 ºC). Yield: 52.2 mg (0.15 mmol, 87%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.98–6.93 (m, 2H), 6.78–6.71 (m, 2H), 3.87–3.72 (m, 1H), 3.34–3.25 (m, 2H), 2.98 (dq, J = 14.1, 7.1 Hz, 1H), 2.53 (dd, J = 13.0, 4.0 Hz, 1H), 2.35 (dd, J = 7.1, 4.6 Hz, 1H), 2.30 (dd, J = 15.3, 5.0 Hz, 1H), 1.85 (t, J = 5.6 Hz, 1H), 1.41 (s, 9H), 1.35 (t, J = 6.8 Hz, 1H), 0.84 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.0, 162.3 (d, J = 246.0 Hz), 156.6, 135.2 (d, J = 3.6 Hz), 127.5 (d, J = 8.1 Hz, +, 2C), 115.7 (d, J = 21.7 Hz, +, 2C), 80.0, 45.0 (–), 43.5 (–), 41.4 (–), 37.3 (+), 35.9, 28.5 (+, 3C), 26.1 (–), 13.5 (+). FTIR (NaCl, cm^{-1}): 2975, 2932, 1699, 1651, 1512, 1476,

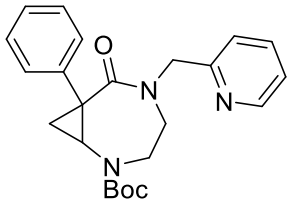
1395, 1366, 1345, 1250, 1234, 1148, 1064, 834, 778. HRMS (TOF ES): found 371.1756, calculated for $C_{19}H_{25}FN_2O_3Na$ (M + Na) 371.1747 (2.4 ppm).



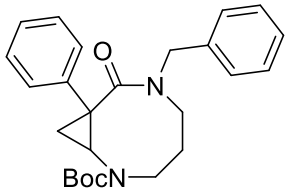
tert-Butyl 7-(3-bromophenyl)-5-isobutyl-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217gf). This compound was synthesized according to Typical Procedure from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (**169g**) (200 mg, 0.84 mmol, 1.0 equiv.), and *tert*-butyl (2-(isobutylamino)ethyl)carbamate (217 mg, 1 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(1-(3-bromophenyl)-*N*-isobutylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ge**) was used at the cyclization step as is without additional purification. To this end, amide **216ge** (60 mg, 0.137 mmol) was treated with powdered KOH (19.2 mg, 0.342 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.48, mp 122-123 °C). Yield: 56.5 mg (0.129 mmol, 94%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.39 (t, *J* = 1.9 Hz, 1H), 7.18–7.15 (m, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.76 (t, *J* = 7.9 Hz, 1H), 3.77 (br.t, *J* = 10.3 Hz, 1H), 3.33–3.20 (m, 2H), 2.65 (dd, *J* = 13.4, 8.2 Hz, 1H), 2.51–2.43 (m, 1H), 2.37–2.29 (m, 2H), 1.84 (t, *J* = 5.7 Hz, 1H), 1.67 (dh, *J* = 8.1, 6.7 Hz, 1H), 1.41 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 1H), 0.75 (dd, *J* = 6.7, 1.1 Hz, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.1, 156.4, 142.1, 130.5 (+), 130.1 (+), 128.7 (+), 124.8 (+), 123.3, 80.1, 53.8 (–), 44.5 (–), 44.4 (–), 37.2 (+), 36.4, 28.4 (+, 3C), 28.0 (+), 26.6 (–), 20.3 (+), 20.1 (+). FTIR (NaCl, cm^{-1}): 2964, 2928, 2871, 1702, 1652, 1593, 1562, 1477, 1428, 1367, 1345, 1297, 1248, 1247, 1175, 1062, 856, 777, 693, 664. HRMS (TOF ES): found 459.1263, calculated for $C_{21}H_{29}BrN_2O_3Na$ (M + Na) 459.1259 (0.9 ppm).



tert-Butyl 8-(3-bromophenyl)-6-(4-fluorobenzyl)-7-oxo-2,6-diazabicyclo[6.1.0]nonane-2-carboxylate (217gh). This compound was synthesized according to Typical Procedure from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (**217g**) (200 mg, 0.84 mmol, 1.0 equiv.), and *tert*-butyl (3-((4-fluorobenzyl)amino)propyl)carbamate (283 mg, 1 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (3-(1-(3-bromophenyl)-*N*-(4-fluorobenzyl)cycloprop-2-ene-1-carboxamido)propyl)carbamate (**216gh**) was used at the cyclization step as is without additional purification. To this end, amide **217gh** (60 mg, 0.119 mmol) was treated with powdered KOH (16.7 mg, 0.298 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:1) as a colorless solid (R_f 0.27, mp 119-121 °C). Yield: 54.1 mg (0.107 mmol, 90%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.32 (s, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 6.97 (dd, *J* = 8.1, 5.7 Hz, 2H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.79 (t, *J* = 8.6 Hz, 2H), 6.68 (t, *J* = 7.9 Hz, 1H), 5.01 (d, *J* = 14.6 Hz, 1H), 3.86 (d, *J* = 14.3 Hz, 1H), 3.59 (d, *J* = 14.6 Hz, 1H), 3.28 (dd, *J* = 15.5, 11.2 Hz, 1H), 2.80–2.69 (m, 2H), 2.51 (dd, *J* = 15.5, 5.9 Hz, 1H), 2.41 (ddd, *J* = 14.6, 11.5, 3.2 Hz, 1H), 1.68–1.56 (m, 1H), 1.43 (s, 9H), 1.19 (dd, *J* = 8.5, 6.6 Hz, 1H), 0.92–0.82 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 162.8 (d, *J* = 245.3 Hz), 155.2, 143.3, 134.2 (d, *J* = 3.5 Hz), 130.5 (+), 130.3 (d, *J* = 8.1 Hz, +, 2C), 129.9 (+), 128.7 (+), 124.2 (+), 123.5, 115.7 (d, *J* = 21.1 Hz, +, 2C), 80.2, 50.3 (–), 48.7 (–), 46.6 (+), 46.2 (–), 37.0, 28.5 (+, 3C), 27.6 (–), 25.2 (–). FTIR (NaCl, cm^{-1}): 2973, 2925, 1692, 1639, 1593, 1562, 1509, 1477, 1414, 1383, 1367, 1256, 1221, 1154, 1107, 969, 858, 819, 769, 689. HRMS (TOF ES): found 525.1165, calculated for $C_{25}H_{28}BrFN_2O_3Na$ (M + Na) 525.1165 (0.0 ppm).

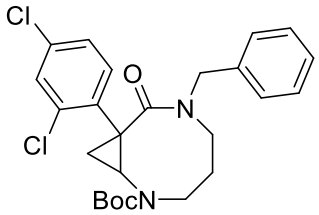


tert-Butyl 6-oxo-7-phenyl-5-(pyridin-2-ylmethyl)-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ag). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**169a**) (200 mg, 1.25 mmol, 1.0 equiv.), and *tert*-butyl (2-((pyridin-2-ylmethyl)amino)ethyl)carbamate (377 mg, 1.5 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(1-phenyl-*N*-(pyridin-2-ylmethyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ag**) was used at the cyclization step as is without additional purification. To this end, amide **216ag** (60 mg, 0.152 mmol) was treated with powdered KOH (21.4 mg, 0.381 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:2) as a colorless glass (R_f 0.31). Yield: 48.6 mg (0.123 mmol, 81%). ^{1}H NMR (500 MHz, C_6D_6) δ 8.37 (d, *J* = 4.8 Hz, 1H), 7.16 (s, 4H), 7.12–6.98 (m, 3H), 6.66–6.59 (m, 1H), 4.65 (br.s, 2H), 3.65 (br.s, 1H), 3.51 (td, *J* = 14.8, 14.2, 3.8 Hz, 1H), 2.88 (dd, *J* = 15.2, 4.9 Hz, 1H), 2.47–2.38 (m, 2H), 1.94 (t, *J* = 5.6 Hz, 1H), 1.53 (t, *J* = 6.8 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.8, 158.4, 159.4, 149.3 (+), 139.4, 136.4 (+), 128.9 (+, 2C), 128.1, 126.9 (+), 125.8 (+, 2C), 122.8 (+), 122.3 (+), 79.8, 52.2 (–), 44.6 (–), 44.6 (–), 37.7 (+), 36.2, 28.4 (+, 3C), 26.3 (–). FTIR (NaCl, cm^{-1}): 2961, 2924, 2854, 1700, 1654, 1591, 1474, 1435, 1394, 1366, 1345, 1251, 1146, 1066, 756, 698, 610. HRMS (TOF ES): found 416.1958, calculated for $C_{23}H_{27}N_3O_3Na$ (M + Na) 416.195 (1.9 ppm).



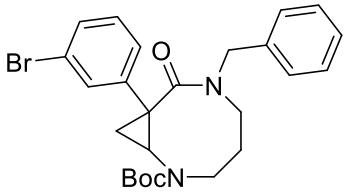
tert-Butyl 6-benzyl-7-oxo-8-phenyl-2,6-diazabicyclo[6.1.0]nonane-2-carboxylate (217ah). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**H-acid**) (200 mg, 1.25 mmol, 1.0 equiv.), and *tert*-butyl (3-(benzylamino)propyl)carbamate (396 mg,

1.5 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (3-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propyl)carbamate (**216ah**) was used at the cyclization step as is without additional purification. To this end, amide **216ah** (60 mg, 0.148 mmol) was treated with powdered KOH (20.7 mg, 0.369 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.21, mp 110-112 °C). Yield: 50.5 mg (0.124 mmol, 84%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.18–7.16 (m, 4H), 7.13–6.98 (m, 6H), 5.19 (d, *J* = 14.7 Hz, 1H), 3.89 (br.d, *J* = 14.6 Hz, 1H), 3.84 (d, *J* = 14.7 Hz, 1H), 3.54 (dd, *J* = 15.3, 11.5 Hz, 1H), 3.03 (dd, *J* = 8.8, 6.0 Hz, 1H), 2.80–2.75 (m, 1H), 2.65 (dd, *J* = 15.4, 5.6 Hz, 1H), 2.59 (ddd, *J* = 14.4, 11.3, 3.2 Hz, 1H), 1.76–1.65 (m, 1H), 1.46 (s, 9H), 1.33 (dd, *J* = 8.8, 6.7 Hz, 1H), 0.98–0.89 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 170.0, 155.3, 140.9, 138.7, 129.0 (+, 2C), 128.8 (+, 2C), 128.6 (+, 2C), 127.5 (+), 126.7 (+), 125.9 (+, 2C), 80.0, 49.9 (–), 49.4 (–), 46.2 (+), 46.1 (–), 37.5, 28.5 (+, 3C), 27.6 (–), 24.8 (–). FTIR (NaCl, cm^{-1}): 2925, 2854, 1692, 1640, 1631, 1585, 1470, 1453, 1416, 1383, 1366, 1288, 1253, 1156, 1105, 1051, 939, 860, 788, 732, 699. HRMS (TOF ES): found 429.2164, calculated for $C_{25}H_{30}N_2O_3Na$ (M + Na) 429.2154 (2.3 ppm).



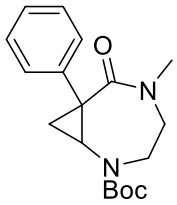
tert-Butyl 6-benzyl-8-(2,4-dichlorophenyl)-7-oxo-2,6-diazabicyclo[6.1.0]nonane-2-carboxylate (217ch). This compound was synthesized according to Typical Procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**169c**) (200 mg, 0.87 mmol, 1.0 equiv.), and *tert*-butyl (3-(benzylamino)propyl)carbamate (278 mg, 1.05 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (3-(*N*-benzyl-1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxamido)propyl)carbamate (**216ch**) was used at the cyclization step as is without

additional purification. To this end, amide **216ch** (60 mg, 0.126 mmol) was treated with powdered KOH (17.7 mg, 0.316 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.24, mp 118-120 °C). Yield: 51.5 mg (0.108 mmol, 86%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.48 (d, *J* = 8.5 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.04–6.93 (m, 5H), 6.84 (dd, *J* = 8.4, 2.2 Hz, 1H), 5.01 (d, *J* = 14.9 Hz, 1H), 4.11 (t, *J* = 13.6 Hz, 1H), 3.88–3.73 (m, 2H), 3.20–3.06 (m, 2H), 2.71–2.63 (m, 1H), 2.30 (t, *J* = 6.5 Hz, 1H), 1.47 (s, 9H), 1.39–1.31 (m, 1H), 1.12 (dd, *J* = 8.9, 6.5 Hz, 1H), 0.99–0.85 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.7, 155.3, 138.4, 137.4, 135.2, 134.2 (+), 134.0, 130.4 (+), 128.8 (+, 2C), 128.2 (+, 2C), 127.5 (+), 127.5 (+), 80.2, 49.9 (–), 45.2 (+), 44.7 (–), 44.0 (–), 35.7, 28.5 (+, 3C), 27.8 (–), 21.3 (–). FTIR (NaCl, cm^{-1}): 2972, 2925, 2854, 1690, 1639, 1477, 1454, 1423, 1383, 1366, 1292, 1255, 1159, 1106, 1078, 1059, 968, 860, 750, 733, 699, 602. HRMS (TOF ES): found 497.1382, calculated for $C_{25}H_{28}Cl_2N_2O_3Na$ (M + Na) 497.1375 (1.4 ppm).



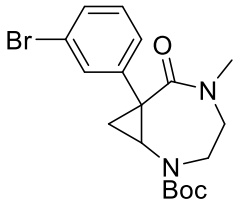
tert-Butyl 6-benzyl-8-(3-bromophenyl)-7-oxo-2,6-diazabicyclo[6.1.0]nonane-2-carboxylate (217gh). This compound was synthesized according to Typical Procedure from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (**169g**) (200 mg, 0.84 mmol, 1.0 equiv.), and *tert*-butyl (3-(benzylamino)propyl)carbamate (267 mg, 1 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (3-(*N*-benzyl-1-(3-bromophenyl)cycloprop-2-ene-1-carboxamido)propyl)carbamate (**216gh**) was used at the cyclization step as is without additional purification. To this end, amide **216gh** (60 mg, 0.124 mmol) was treated with powdered KOH (17.3 mg, 0.308 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product

was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.24, mp 121-123 °C). Yield: 49.8 mg (0.103 mmol, 83%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.39 (s, 1H), 7.16–7.11 (m, 5H), 7.06 (t, *J* = 6.7 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.71 (t, *J* = 7.9 Hz, 1H), 5.19 (d, *J* = 14.7 Hz, 1H), 3.87 (br.d, *J* = 14.3 Hz, 1H), 3.73 (d, *J* = 14.7 Hz, 1H), 3.32 (dd, *J* = 15.5, 11.1 Hz, 1H), 2.80 (dd, *J* = 8.3, 6.3 Hz, 1H), 2.75 (t, *J* = 6.3 Hz, 1H), 2.61 (dd, *J* = 15.2, 5.7 Hz, 1H), 2.43 (ddd, *J* = 14.4, 11.6, 3.0 Hz, 1H), 1.73–1.61 (m, 1H), 1.45 (s, 9H), 1.21 (dd, *J* = 8.6, 6.7 Hz, 1H), 0.92–0.84 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 155.2, 143.4, 138.4, 130.5 (+), 129.9 (+), 128.9 (+, 2C), 128.7 (+), 128.6 (+, 2C), 127.6 (+), 124.3 (+), 123.4, 80.2, 50.2 (–), 49.4 (–), 46.6 (+), 46.1 (–), 37.1, 28.5 (+, 3C), 27.5 (–), 25.3 (–). FTIR (NaCl, cm^{-1}): 2972, 2925, 1691, 1639, 1593, 1561, 1476, 1454, 1418, 1383, 1366, 1282, 1256, 1158, 1106, 1078, 968, 860, 768, 752, 700. HRMS (TOF ES): found 507.1255, calculated for $C_{25}H_{29}BrN_2O_3Na$ (M + Na) 507.1259 (0.8 ppm).



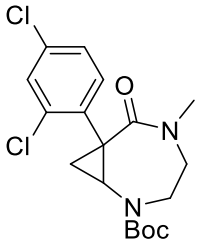
tert-Butyl 5-methyl-6-oxo-7-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ad). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**169a**) (200 mg, 1.25 mmol, 1.0 equiv.), and *tert*-butyl (2-(methylamino)ethyl)carbamate (261 mg, 1.5 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-methyl-1-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ad**) was used at the cyclization step as is without additional purification. To this end, amide **216ad** (60 mg, 0.19 mmol) was treated with powdered KOH (26.6 mg, 0.474 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.42, mp 188-189 °C). Yield: 54.6 mg (0.173 mmol, 91%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.15–7.06 (m, 4H), 7.03 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.79 (br.t, *J* = 11.4 Hz, 1H), 3.43 (ddd, *J* = 15.5, 13.7, 3.7 Hz, 1H), 2.58 (s, 3H), 2.52–2.43 (m, 2H), 2.17 (dd, *J* = 15.4, 4.7 Hz, 1H), 1.87 (t, *J* = 5.3 Hz, 1H), 1.46 (t, *J* = 6.7 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.5, 156.7, 139.5, 128.9 (+, 2C), 127.0 (+), 125.9 (+, 2C), 80.0, 45.5 (–), 43.6 (–), 37.3 (+), 36.4, 33.3 (+), 28.5 (+, 3C), 26.3 (–). FTIR (NaCl, cm^{-1}): 2974, 2928, 1698, 1655, 1479, 1432, 1396, 1357, 1345, 1251, 1175, 1146, 1067, 856, 775, 758, 698, 615. HRMS (TOF ES): found 339.1696, calculated for $C_{18}H_{24}N_2O_3Na$ (M + Na) 339.1685 (3.2 ppm).

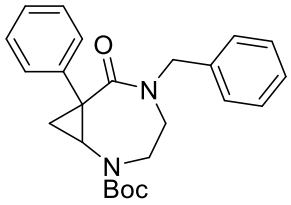


tert-Butyl 7-(3-bromophenyl)-5-methyl-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217gd). This compound was synthesized according to Typical Procedure from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (**169g**) (200 mg, 0.84 mmol, 1.0 equiv.), and *tert*-butyl (2-(methylamino)ethyl)carbamate (175 mg, 1 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(1-(3-bromophenyl)-*N*-methylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216gd**) was used at the cyclization step as is without additional purification. To this end, amide **216gd** (60 mg, 0.152 mmol) was treated with powdered KOH (21.3 mg, 0.38 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless solid (R_f 0.39, mp 115-117 °C). Yield: 54.1 mg (0.137 mmol, 90%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.36–7.31 (m, 1H), 7.19–7.15 (m, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.75 (t, *J* = 7.9 Hz, 1H), 3.72 (br.t, *J* = 10.6 Hz, 1H), 3.34–3.23 (m, 1H), 2.52 (s, 3H), 2.42 (dd, *J* = 13.1, 3.8 Hz, 1H), 2.33–2.28 (m, 1H), 2.13 (dd, *J* = 15.3, 4.4 Hz, 1H), 1.80 (t, *J* = 5.6 Hz, 1H), 1.40 (s, 9H), 1.31 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 168.9, 156.6, 142.0, 130.5 (+), 130.2 (+), 128.6 (+), 125.1 (+), 123.3,

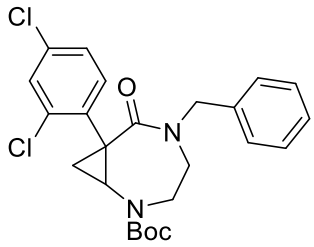
80.1, 45.4 (–), 43.5 (–), 37.0 (+), 36.1, 33.3 (+), 28.4 (+, 3C), 26.4 (–). FTIR (NaCl, cm^{-1}): 2974, 2928, 1699, 1657, 1593, 1563, 1478, 1394, 1356, 1342, 1250, 1174, 1147, 1082, 1054, 856, 778, 695, 664. HRMS (TOF ES): found 417.0786, calculated for $C_{18}H_{23}BrN_2O_3Na$ (M + Na) 417.0790 (1.0 ppm).



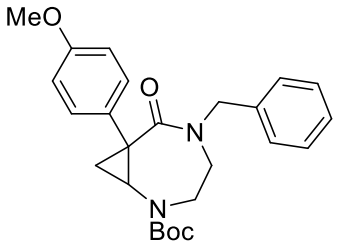
tert-Butyl 7-(2,4-dichlorophenyl)-5-methyl-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (216cd). This compound was synthesized according to Typical Procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**169c**) (200 mg, 0.87 mmol, 1.0 equiv.), and *tert*-butyl (2-(methylamino)ethyl)carbamate (183 mg, 1.05 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(1-(2,4-dichlorophenyl)-*N*-methylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216cd**) was used at the cyclization step as is without additional purification. To this end, amide **216cd** (60 mg, 0.156 mmol) was treated with powdered KOH (21.8 mg, 0.389 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless solid (R_f 0.42, mp 180-181 ^{o}C). Yield: 52.2 mg (0.136 mmol, 87%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.48 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.5, 2.0 Hz, 1H), 4.16–4.06 (m, 1H), 3.82 (br.t, J = 11.7 Hz, 1H), 2.99–2.95 (m, 1H), 2.78–2.72 (m, 1H), 2.48 (s, 3H), 2.27 (dd, J = 15.4, 4.4 Hz, 1H), 1.73 (br.s, 1H), 1.40 (s, 9H), 1.27 (br.s, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 168.7, 156.6, 135.3, 134.8, 134.4 (+), 134.0, 130.7 (+), 127.4 (+), 80.1, 45.3 (–), 43.8 (–), 36.0 (+), 35.6, 34.2 (+), 28.4 (+, 3C), 26.3 (–). FTIR (NaCl, cm^{-1}): 2974, 2929, 1700, 1656, 1474, 1428, 1380, 1366, 1277, 1253, 1174, 1145, 1107, 1079, 858, 829, 781. HRMS (TOF ES): found 407.0921, calculated for $C_{18}H_{22}Cl_2N_2O_3Na$ (M + Na) 407.0905 (3.9 ppm).



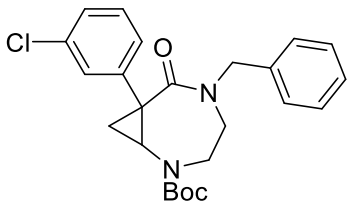
tert-Butyl 5-benzyl-6-oxo-7-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217aa). This compound was synthesized according to Typical Procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**169a**) (200 mg, 1.25 mmol, 1.0 equiv.), and *tert*-butyl (2-(benzylamino)ethyl)carbamate (375 mg, 1.5 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216aa**) was used at the cyclization step as is without additional purification. To this end, amide **216aa** (60 mg, 0.153 mmol) was treated with powdered KOH (21.4 mg, 0.381 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:1) as a colorless solid (R_f 0.3, mp 103-105 °C). Yield: 51.7 mg (0.132 mmol, 86%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.19–7.14 (m, 3H), 7.14–7.06 (m, 5H), 7.08–7.00 (m, 2H), 4.53 (br.s, 1H), 4.29 (br.s, 1H), 3.56 (br.s, 1H), 3.39 (td, *J* = 13.4, 4.0 Hz, 1H), 2.54–2.45 (m, 2H), 2.41 (dd, *J* = 12.8, 3.9 Hz, 1H), 1.97 (t, *J* = 5.6 Hz, 1H), 1.52 (t, *J* = 6.9 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.9, 156.5, 139.4, 138.4, 129.0 (+, 2C), 128.9 (+, 2C), 128.4 (+, 2C), 127.6 (+), 127.0 (+), 125.8 (+, 2C), 79.9, 49.6 (–), 44.5 (–), 43.4 (–), 37.4 (+), 36.4, 28.4 (+, 3C), 26.5 (–). FTIR (NaCl, cm^{-1}): 2975, 2928, 1701, 1652, 1496, 1470, 1425, 1394, 1366, 1346, 1250, 1146, 1065, 1029, 987, 856, 811, 750, 698, 632, 606. HRMS (TOF ES): found 415.2008, calculated for $C_{24}H_{28}N_2O_3Na$ (M + Na) 415.1998 (2.4 ppm).



tert-Butyl 5-benzyl-7-(2,4-dichlorophenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ca). This compound was synthesized according to Typical Procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**169c**) (200 mg, 0.87 mmol, 1.0 equiv.), and *tert*-butyl (2-(benzylamino)ethyl)carbamate (262 mg, 1.05 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-benzyl-1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ca**) was used at the cyclization step as is without additional purification. To this end, amide **216ca** (60 mg, 0.13 mmol) was treated with powdered KOH (18.2 mg, 0.324 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:1) as a colorless solid (R_f 0.33, mp 92-93 ºC). Yield: 50.9 mg (0.11 mmol, 85%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.53 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.06–6.97 (m, 5H), 6.86 (dd, *J* = 8.5, 2.3 Hz, 1H), 4.34 (br.s, 1H), 4.28 (br.s, 1H), 4.09 (td, *J* = 13.2, 3.7 Hz, 1H), 3.61 (br.s, 1H), 2.99 (dd, *J* = 7.2, 4.4 Hz, 1H), 2.72–2.64 (m, 1H), 2.61–2.53 (m, 1H), 1.84 (t, *J* = 5.4 Hz, 1H), 1.41 (s, 9H), 1.38–1.34 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 156.4, 138.0, 135.3, 134.8, 134.5 (+), 134.1, 130.8 (+), 128.9 (+, 2C), 128.2 (+, 2C), 127.7 (+), 127.5 (+), 80.0, 50.4 (–), 44.5 (–), 43.2 (–), 36.3 (+), 35.7, 28.4 (+, 3C), 26.4 (–). FTIR (NaCl, cm^{-1}): 2973, 2927, 1701, 1653, 1585, 1473, 1419, 1392, 1366, 1346, 1253, 1168, 1145, 1107, 1078, 1046, 992, 858, 820, 784, 734, 700. HRMS (TOF ES): found 483.1214, calculated for $C_{24}H_{26}Cl_2N_2O_3Na$ (M + Na) 483.1218 (0.8 ppm).

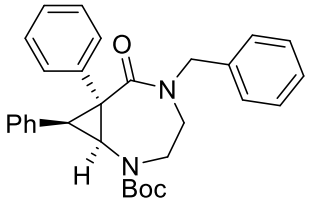


tert-Butyl 5-benzyl-7-(4-methoxyphenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ea). This compound was synthesized according to Typical Procedure from 1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxylic acid (**169e**) (200 mg, 1.05 mmol, 1.0 equiv.), and *tert*-butyl (2-(benzylamino)ethyl)carbamate (316 mg, 1.26 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-benzyl-1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ea**) was used at the cyclization step as is without additional purification. To this end, amide **216ea** (60 mg, 0.142 mmol) was treated with powdered KOH (19.9 mg, 0.355 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (3:1) as a colorless solid (R_f 0.26, mp 103-105 ºC). Yield: 51.5 mg (0.122 mmol, 86%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.15–7.07 (m, 6H), 7.07–7.02 (m, 1H), 6.77–6.73 (m, 2H), 4.60 (br.s, 1H), 4.25 (br.s, 1H), 3.61 (br.s, 1H), 3.51 (td, *J* = 14.4, 2.2 Hz, 1H), 3.33 (s, 3H), 2.58–2.41 (m, 3H), 1.96 (t, *J* = 5.4 Hz, 1H), 1.50 (t, *J* = 6.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 170.2, 159.3, 156.6, 138.5, 131.2, 128.9 (+, 2C), 128.3 (+, 2C), 127.6 (+), 127.2 (+, 2C), 114.7 (+, 2C), 79.8, 55.0 (+), 49.5 (–), 44.6 (–), 43.4 (–), 36.8 (+), 35.9, 28.5 (+, 3C), 26.1 (–). FTIR (NaCl, cm^{-1}): 2974, 2928, 1700, 1651, 1515, 1496, 1428, 1393, 1366, 1346, 1250, 1179, 1146, 1065, 1030, 829, 777, 731, 701. HRMS (TOF ES): found 445.2098, calculated for $C_{25}H_{30}N_2O_4Na$ (M + Na) 445.2103 (1.1 ppm).



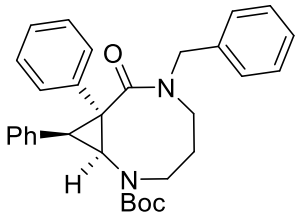
tert-Butyl 5-benzyl-7-(3-chlorophenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217fa). This compound was synthesized according to Typical Procedure from 1-(3-

chlorophenyl)cycloprop-2-ene-1-carboxylic acid (**169f**) (200 mg, 1.03 mmol, 1.0 equiv.), and *tert*-butyl (2-(benzylamino)ethyl)carbamate (309 mg, 1.23 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-benzyl-1-(3-chlorophenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216fa**) was used at the cyclization step as is without additional purification. To this end, amide **216fa** (60 mg, 0.141 mmol) was treated with powdered KOH (19.7 mg, 0.351 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (1:1) as a colorless solid (R_f 0.4, mp 100-102 ºC). Yield: 52.9 mg (0.124 mmol, 88%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.21 (s, 1H), 7.1–7.1 (m, 4H), 7.05 (t, *J* = 6.4 Hz, 1H), 7.02–6.98 (m, 2H), 6.81 (t, *J* = 7.9 Hz, 1H), 4.50 (br.s, 1H), 4.19 (br.s, 1H), 3.51 (br.s, 1H), 3.22 (td, *J* = 13.3, 4.1 Hz, 1H), 2.44 (dd, *J* = 15.5, 5.0 Hz, 1H), 2.35 (dd, *J* = 12.9, 4.0 Hz, 1H), 2.31 (dd, *J* = 7.2, 4.7 Hz, 1H), 1.92 (t, *J* = 5.7 Hz, 1H), 1.41 (s, 9H), 1.39–1.29 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 156.3, 141.7, 138.2, 135.2, 130.2 (+), 128.9 (+, 2C), 128.4 (+, 2C), 127.7 (+), 127.2 (+), 125.8 (+), 124.3 (+), 80.0, 49.6 (–), 44.3 (–), 43.4 (–), 37.4 (+), 36.1, 28.4 (+, 3C), 26.6 (–). FTIR (NaCl, cm^{-1}): 2974, 2926, 2855, 1699, 1651, 1593, 1510, 1478, 1392, 1366, 1344, 1248, 1223, 1148, 1065, 993, 852, 815, 777, 736. HRMS (TOF ES): found 449.1618, calculated for $C_{24}H_{27}ClN_2O_3Na$ (M + Na) 449.1608 (1.0 ppm).



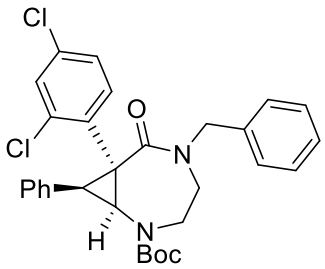
tert-Butyl (1R*,7R*,8R*)-5-benzyl-6-oxo-7,8-diphenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ha). This compound was synthesized according to Typical Procedure from 1,2-diphenylcycloprop-2-ene-1-carboxylic acid (**169h**) (150 mg, 0.63 mmol, 1.0 equiv.), and *tert*-butyl (2-(benzylamino)ethyl)carbamate (191 mg, 0.76 mmol, 1.2 equiv.). After extraction and filtration

through a silica plug crude *tert*-butyl (2-(*N*-benzyl-1,2-diphenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ha**) was used at the cyclization step as is without additional purification. To this end, amide **216ha** (50 mg, 0.107 mmol) was treated with powdered KOH (15 mg, 0.267 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.43, mp 183-184 °C). Yield: 45.6 mg (0.097 mmol, 91%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.31 (d, *J* = 7.6 Hz, 2H), 7.20 (br. s, 2H), 7.10–6.98 (m, 5H), 6.96 (t, *J* = 7.6 Hz, 4H), 6.87 (t, *J* = 7.3 Hz, 2H), 4.51 (br. s, 1H), 4.25 (br. s, 1H), 3.80–3.56 (m, 2H), 3.37 (d, *J* = 4.7 Hz, 1H), 3.22 (d, *J* = 4.7 Hz, 1H), 2.62 (d, *J* = 9.2 Hz, 1H), 2.49 (d, *J* = 10.6 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 170.3, 156.9, 138.2, 136.1, 134.7, 129.4 (+, 2C), 128.8 (+, 2C), 128.8 (+, 2C), 128.6 (+, 2C), 128.4 (+, 2C), 128.0 (+, 2C), 127.6 (+), 127.4 (+), 126.6 (+), 80.2, 49.8 (–), 44.6 (–), 44.6, 43.1 (–), 40.9 (+), 39.1 (+), 28.5 (+, 3C). FTIR (NaCl, cm^{-1}): 2976, 2926, 2868, 1701, 1647, 1496, 1469, 1423, 1363, 1252, 1170, 1142, 777, 735, 698. HRMS (TOF ES): found 491.2318, calculated for $C_{30}H_{32}N_2O_3Na$ (M + Na) 491.2311 (1.4 ppm).



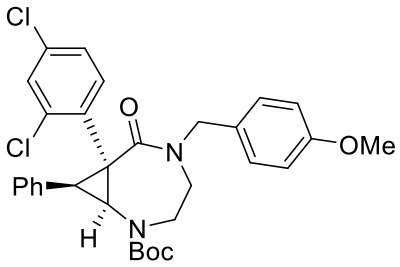
tert-butyl (1R*,8R*,9R*)-6-benzyl-7-oxo-8,9-diphenyl-2,6-diazabicyclo[6.1.0]nonane-2-carboxylate (217hh). This compound was synthesized according to Typical Procedure from 1,2-diphenylcycloprop-2-ene-1-carboxylic acid (**169h**) (150 mg, 0.63 mmol, 1.0 equiv.), and *tert*-butyl (3-(benzylamino)propyl)carbamate (202 mg, 0.76 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (3-(*N*-benzyl-1,2-diphenylcycloprop-2-ene-1-carboxamido)propyl)carbamate (**216hi**) was used at the cyclization step as is without additional purification. To this end, amide **216hi** (50 mg, 0.104 mmol) was treated with powdered KOH (14.5

mg, 0.258 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f 0.4, mp 98-99 ºC). Yield: 43.9 mg (0.091 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.17 (m, 15H), 5.39 (d, *J* = 15.0 Hz, 1H), 4.20 (d, *J* = 15.0 Hz, 1H), 4.22 (br. s, 1H), 4.09 (dd, *J* = 15.3, 11.5 Hz, 1H), 4.05 (br. s, 1H), 3.78 (d, *J* = 6.5 Hz, 1H), 3.54 (ddd, *J* = 14.2, 9.7, 3.2 Hz, 1H), 3.19 (ddd, *J* = 15.4, 5.3, 2.3 Hz, 1H), 2.08–1.97 (m, 1H), 1.89–1.78 (m, 1H), 1.60 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 156.2, 137.5, 135.8, 135.2, 128.8 (+, 2C), 128.6 (+, 2C), 128.4 (+, 4C), 127.9 (+, 4C), 127.4 (+), 127.2 (+), 126.3 (+), 80.9, 49.4 (–, 2C), 47.7 (+), 45.7 (–), 45.4, 36.8 (+), 28.6 (+, 3C), 28.3 (–). FTIR (NaCl, cm^{-1}): 2976, 2928, 1694, 1634, 1477, 1417, 1365, 1294, 1258, 1155, 1078, 735, 698. HRMS (TOF ES): found 505.2472, calculated for $C_{31}H_{34}N_2O_3Na$ (M + Na) 505.2467 (1.0 ppm).



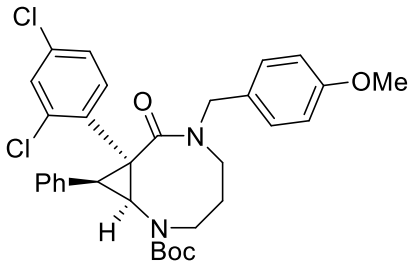
tert-butyl (1R*,7R*,8R*)-5-benzyl-7-(2,4-dichlorophenyl)-6-oxo-8-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ia). This compound was synthesized according to Typical Procedure from 1-(2,4-dichlorophenyl)-2-phenylcycloprop-2-ene-1-carboxylic acid (**169i**) (150 mg, 0.49 mmol, 1.0 equiv.), and *tert*-butyl (2-(benzylamino)ethyl)carbamate (148 mg, 0.59 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(*N*-benzyl-1-(2,4-dichlorophenyl)-2-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ia**) was used at the cyclization step as is without additional purification. To this end, amide **216ia** (50 mg, 0.093 mmol) was treated with powdered KOH (13 mg, 0.232 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (4:1) as a colorless glass (R_f 0.33). Yield: 38.5 mg (0.072

mmol, 77%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.71 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 9.7 Hz, 6H), 6.97–6.89 (m, 4H), 6.89–6.79 (m, 1H), 6.71–6.55 (m, 1H), 4.48–4.27 (m, 3H), 3.93 (d, *J* = 4.8 Hz, 1H), 3.78 (br. s, 1H), 3.20 (br. s, 1H), 2.85–2.80 (m, 1H), 2.64 (dd, *J* = 15.6, 5.3 Hz, 1H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.8, 156.6, 137.8, 136.6 (+), 136.3, 134.6, 134.2, 130.6, 130.4 (+), 128.9 (+, 2C), 128.6 (+, 2C), 128.2 (+, 2C), 128.2 (+, 2C), 127.7 (+), 127.6 (+), 126.8 (+), 80.2, 50.5 (–), 44.3 (–), 44.3, 43.0 (–), 42.2 (+), 41.1 (+), 28.4 (+, 3C). FTIR (NaCl, cm^{-1}): 2974, 2926, 2864, 1701, 1649, 1473, 1386, 1365, 1250, 1142, 812, 736, 696. HRMS (TOF ES): found 559.1539, calculated for $C_{30}H_{30}Cl_2N_2O_3Na$ (M + Na) 559.1531 (1.4 ppm).



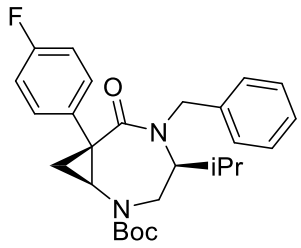
tert-butyl (1R*,7R*,8R*)-7-(2,4-dichlorophenyl)-5-(4-methoxybenzyl)-6-oxo-8-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217ib). This compound was synthesized according to Typical Procedure from 1-(2,4-dichlorophenyl)-2-phenylcycloprop-2-ene-1-carboxylic acid (**169i**) (150 mg, 0.49 mmol, 1.0 equiv.), and *tert*-butyl (2-((4-methoxybenzyl)amino)ethyl)carbamate (165 mg, 0.59 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (2-(1-(2,4-dichlorophenyl)-*N*-(4-methoxybenzyl)-2-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (**216ib**) was used at the cyclization step as is without additional purification. To this end, amide **216ib** (50 mg, 0.088 mmol) was treated with powdered KOH (12.4 mg, 0.221 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (5:1) as a colorless glass (R_f 0.33). Yield: 40.5 mg (0.071 mmol, 81%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.73 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 2.2 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.96–6.90 (m, 4H), 6.85 (ddd, *J* = 8.5, 5.7, 2.3 Hz, 1H), 6.68

(d, *J* = 8.6 Hz, 2H), 6.64 (dd, *J* = 8.6, 2.3 Hz, 1H), 4.36 (ddd, *J* = 15.4, 13.2, 4.4 Hz, 1H), 4.36 (br. s, 2H), 3.93 (d, *J* = 4.7 Hz, 1H), 3.79 (s, 1H), 3.27 (s, 3H), 3.21 (br. s, 1H), 2.85 (dd, *J* = 13.1, 4.2 Hz, 1H), 2.70 (dd, *J* = 15.6, 5.2 Hz, 1H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.7, 159.8, 156.6, 136.6 (+), 136.3, 134.6, 134.2, 130.7, 130.4 (+), 129.8, 129.6 (+, 2C), 128.4 (+, 2C), 128.2 (+, 2C), 127.6 (+), 126.8 (+), 114.6 (+, 2C), 80.2, 54.8 (+), 50.0 (–), 44.4 (–), 44.4, 42.8 (–), 42.2 (+), 41.1 (+), 28.4 (+, 3C). FTIR (NaCl, cm^{-1}): 2974, 2928, 1701, 1647, 1512, 1474, 1364, 1248, 2242, 1035, 810, 769, 736, 696. HRMS (TOF ES): found 589.1639, calculated for $C_{31}H_{32}Cl_2N_2O_4Na$ (M + Na) 589.1637 (0.3 ppm).



tert-butyl (1R*,8R*,9R*)-8-(2,4-dichlorophenyl)-6-(4-methoxybenzyl)-7-oxo-9-phenyl-2,6-diazabicyclo[6.1.0]nonane-2-carboxylate (217ii). This compound was synthesized according to Typical Procedure from 1-(2,4-dichlorophenyl)-2-phenylcycloprop-2-ene-1-carboxylic acid (**169i**) (150 mg, 0.49 mmol, 1.0 equiv.), and *tert*-butyl (3-((4-methoxybenzyl)amino)propyl)carbamate (173 mg, 0.59 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude *tert*-butyl (3-(1-(2,4-dichlorophenyl)-*N*-(4-methoxybenzyl)-2-phenylcycloprop-2-ene-1-carboxamido)propyl)carbamate (**216ii**) was used at the cyclization step as is without additional purification. To this end, amide **216ii** (50 mg, 0.086 mmol) was treated with powdered KOH (12.1 mg, 0.216 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (5:1) as a colorless glass (R_f 0.25). Yield: 37.9 mg (0.065 mmol, 76%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.46 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 2H), 7.04 (d, *J* = 1.7 Hz, 1H), 7.00–6.93 (m, 4H), 6.88 (t, *J* = 7.3 Hz,

1H), 6.64 (d, *J* = 8.5 Hz, 2H), 6.65–6.63 (m, 1H), 5.02 (d, *J* = 14.6 Hz, 1H), 4.61 (br. s, 1H), 4.21 (t, *J* = 13.3 Hz, 2H), 3.91 (br. s, 1H), 3.83 (d, *J* = 14.6 Hz, 1H), 3.47 (br. s, 1H), 3.35 (br. s, 1H), 3.24 (s, 3H), 2.77 (dt, *J* = 15.2, 3.1 Hz, 1H), 1.70–1.27 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 170.1, 159.7, 155.6, 136.3, 135.4 (+), 134.0, 132.6, 130.6 (+), 130.2, 129.6 (+, 2C), 128.4 (+, 2C), 128.4 (+, 2C), 127.2 (+), 126.9 (+), 114.4 (+, 2C), 80.3, 54.8 (+), 49.5 (–), 49.1 (+), 45.0, 44.8 (–, 2C), 37.2 (+), 28.5 (–), 28.5 (+, 3C). FTIR (NaCl, cm^{-1}): 2974, 2928, 1695, 1636, 1512, 1471, 1413, 1365, 1246, 1153, 1105, 1033, 158, 808, 767, 696. HRMS (TOF ES): found 603.1793, calculated for $C_{32}H_{34}Cl_2N_2O_4Na$ (M + Na) 603.1793 (0.0 ppm).



tert-Butyl (1S,4S,7S)-5-benzyl-7-(4-fluorophenyl)-4-isopropyl-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (217bk). This compound was synthesized according to Typical Procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (217b) (100 mg, 0.56 mmol, 1.0 equiv.), and tert-butyl (S)-(2-(benzylamino)-3-methylbutyl)carbamate (197 mg, 0.67 mmol, 1.2 equiv.). After extraction and filtration through a silica plug crude tert-butyl (S)-(2-(N-benzyl-1-(4-fluorophenyl)cycloprop-2-ene-1-carboxamido)-3-methylbutyl)carbamate (216bk) was used at the cyclization step as is without additional purification. To this end, amide 216bk (50 mg, 0.11 mmol) was treated with powdered KOH (15.5 mg, 0.276 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (5:1) as a colorless solid (Rf 0.33, mp 155-157 °C). Yield: 44.6 mg (0.099 mmol, 89%). [α]D20 +97.8 (c = 0.9, CHCl3). 1H NMR (400 MHz, CDCl3) δ 7.32–7.21 (m, 5H), 7.14–7.06 (m, 2H), 7.05–6.97 (m, 2H), 5.44 (br. d, J = 15.1 Hz, 1H), 3.99 (br. d, J = 15.2 Hz, 1H), 3.54 (ddd, J = 12.6, 10.3, 3.9 Hz, 1H), 3.01 (br. s, 1H), 2.86 (dd, J = 12.6, 3.9 Hz, 1H), 2.60 (dd, J = 7.1, 4.6 Hz, 1H), 2.20–2.05 (m, 1H), 1.91 (dd, J = 7.0, 4.6 Hz, 1H), 1.79 (t,

J = 7.1 Hz, 1H), 1.69 (s, 1H), 1.42 (s, 9H), 0.88 (dd, J = 10.1, 6.4 Hz, 6H). 13C NMR (151 MHz, CDCl3) δ 172.1, 161.8 (d, J = 245.8 Hz), 156.4, 138.4, 134.0 (d, J = 3.1 Hz), 128.7 (+, 2C), 127.9 (+), 127.4 (+, 2C), 126.2 (d, J = 8.1 Hz, +, 2C), 115.7 (d, J = 21.5 Hz, +, 2C), 80.5, 61.1 (+), 46.9 (–), 44.3 (–), 39.0 (+), 35.2, 28.3 (+, 3C), 27.4 (–), 21.9 (+, 2C), 19.9 (+). 19F NMR (376 MHz, CDCl3) δ –115.7. FTIR (NaCl, cm-1): 2973, 2929, 1701, 1649, 1513, 1368, 1147, 832, 730. HRMS (TOF ES): found 475.2375, calculated for C27H33FN2O3Na (M + Na) 475.2373 (0.4 ppm). The relative and absolute configuration of compound 217bk was unambiguously confirmed by single-crystal X-ray crystallography (CCDC #1854746).

Appendix

A1. Evaluation of biological activitie of azabicyclo[5.1.0]octanones

The preliminary biological studies were performed by the group of Prof. Frolova (New Mexico Institute of Mining and Technology, Socorro, New Mexico) in the framework of a collaborative project.[3]

MTT assay for mycobacterium abscessus (ATCC 19977). Approximately $5.5 \cdot 10^5$ mycobacteria per mL or a dilution of 1:500 from an overnight growth were plated at a final volume of 400 µL/well in 48-well plates. Compounds were initially screened at a concentration of 100 µM on *M. abscessus*. Compounds with antimycobacterial activity at 100 µM were screened for further activity by adding the selected compounds to cells at a concentration of 50 µM and 2-fold serially diluting. The plates were incubated in a shaking incubator for 48 h at 37 °C. Following the incubation, 40 µL or 10% w/v of MTT reagent (5 mg/mL) was added to each of the wells. The plates were incubated for 2 h at 37 °C. An amount of 650 µL of solubilization solution was added to each of the wells, and the plate was incubated at 37 °C for an additional 12 h. An amount of 100 µL from each well was transferred into a clear 96-well microtiter plate, and A595 was read in a Thermomax Molecular Device plate reader. Wells containing Middlebrook 7H9 medium and nontreated cells served as negative controls, and a well containing 10 µM phenyl arsine oxide treated cells (PAO) served as a positive kill control. The experiments were performed in triplicate.

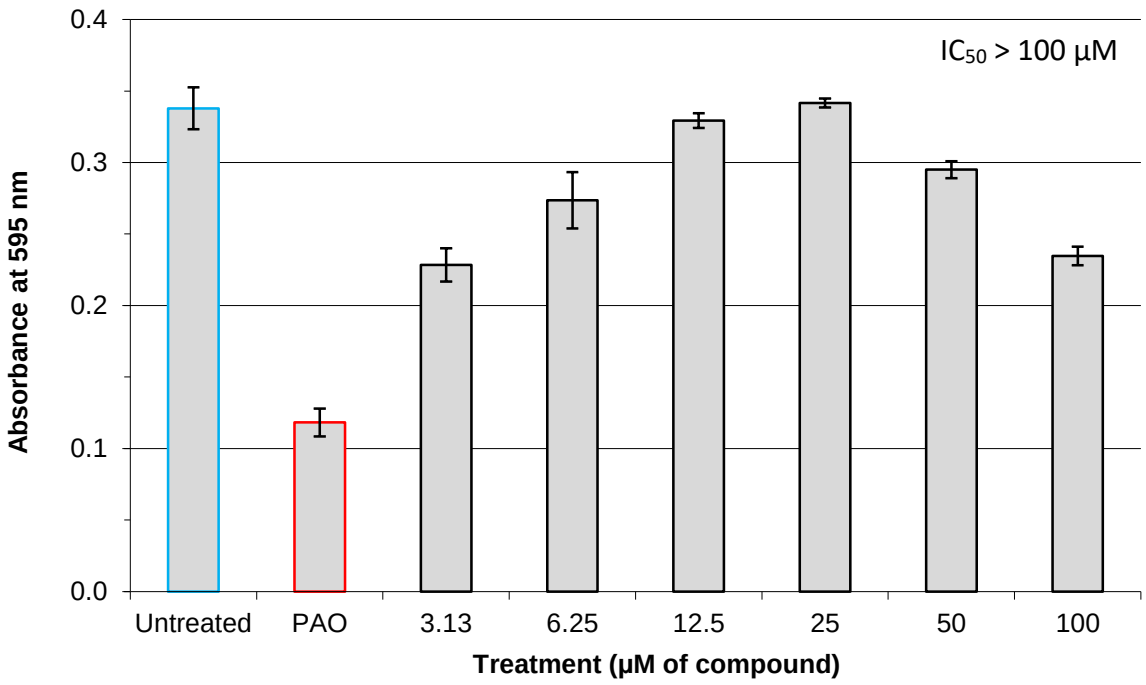
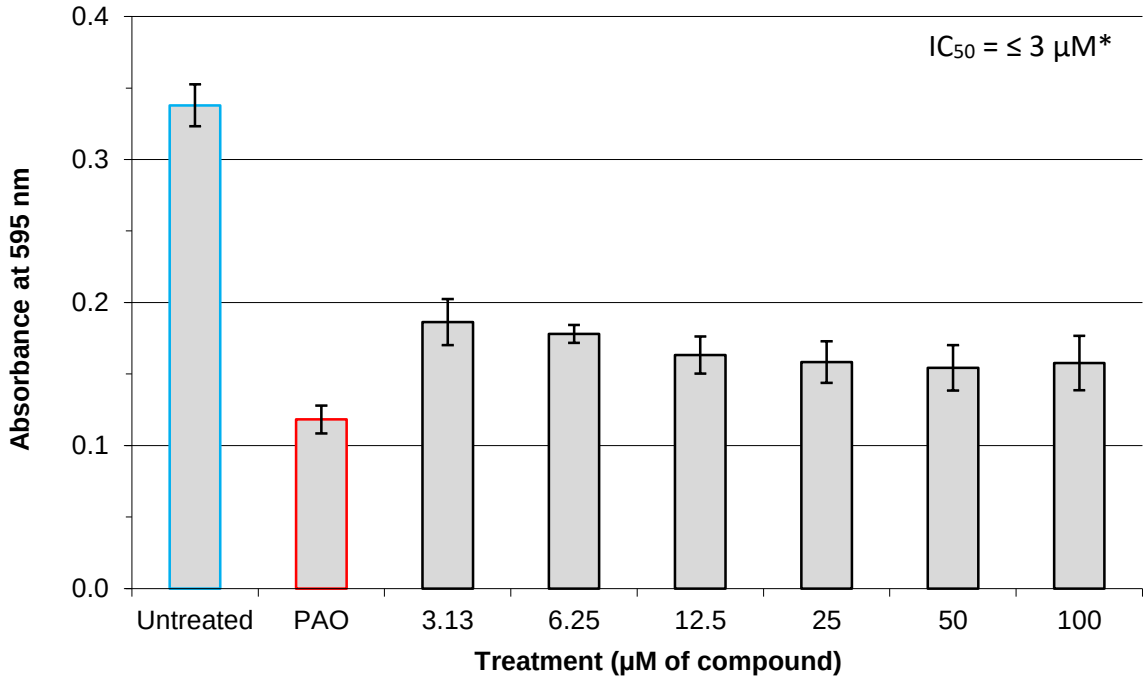


Figure 16. Cytotoxicity of **201aa** towards *mycobacterium abscessus*



** >50% reduction in viability was observed at 3 µM treatment for compound **201ab**, but the absence of data at lower concentrations prevented determination of an accurate IC_{50} value.*
Additionally, only very slight reductions in viability were observed upon treatment with higher concentrations of the compound

Figure 17 Cytotoxicity of **201ab** towards *mycobacterium abscessus*

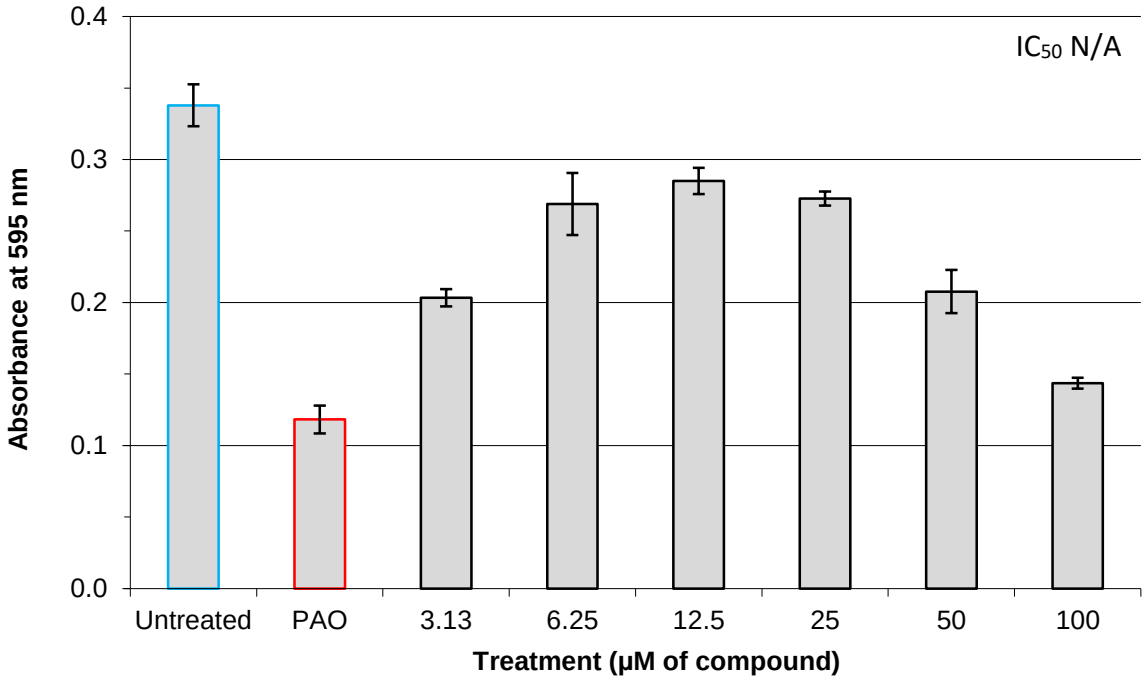


Figure 18 Cytotoxicity of **201ad** towards *mycobacterium abscessus*

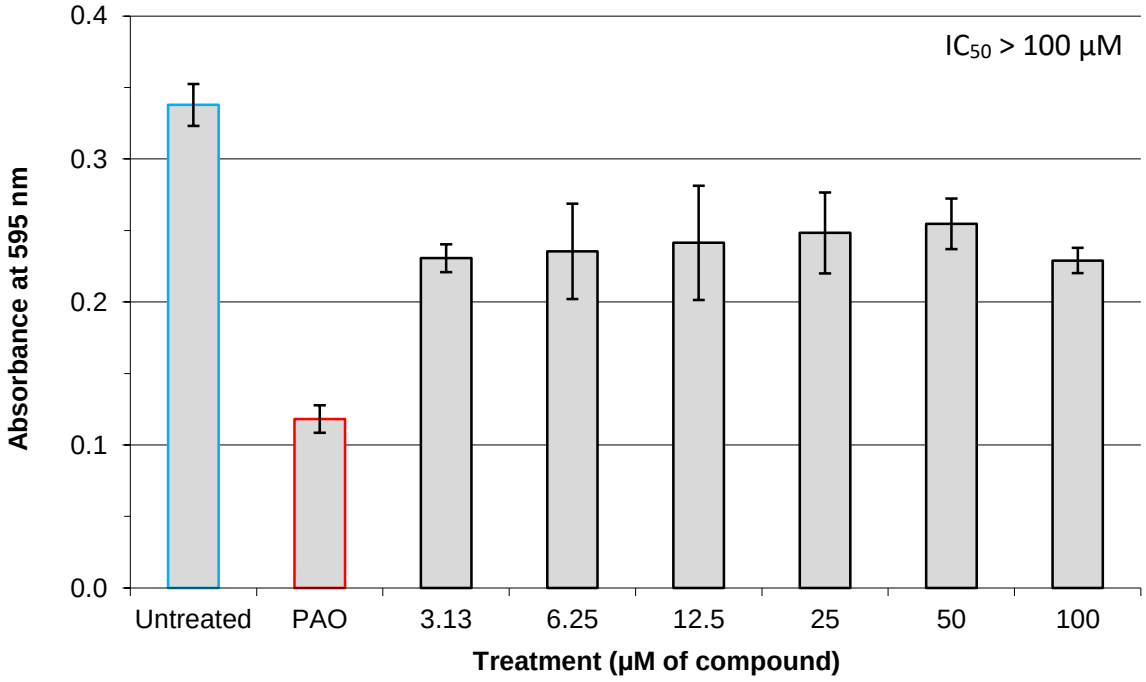
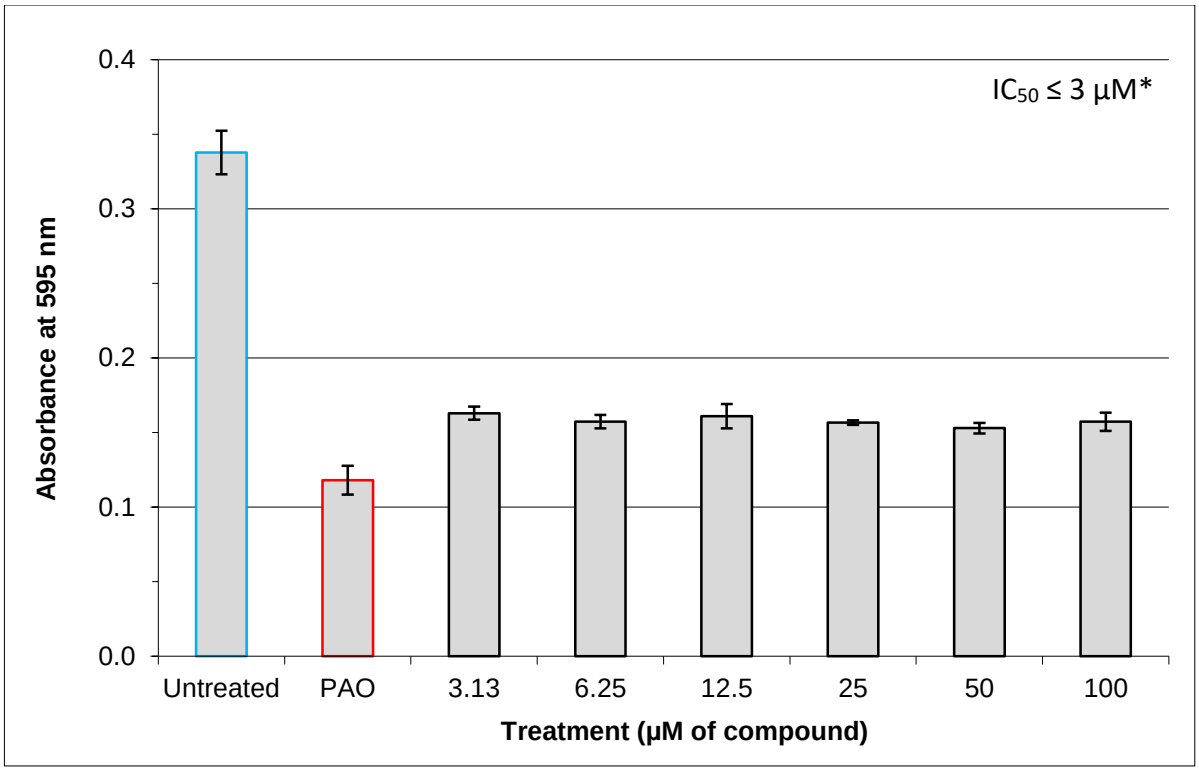
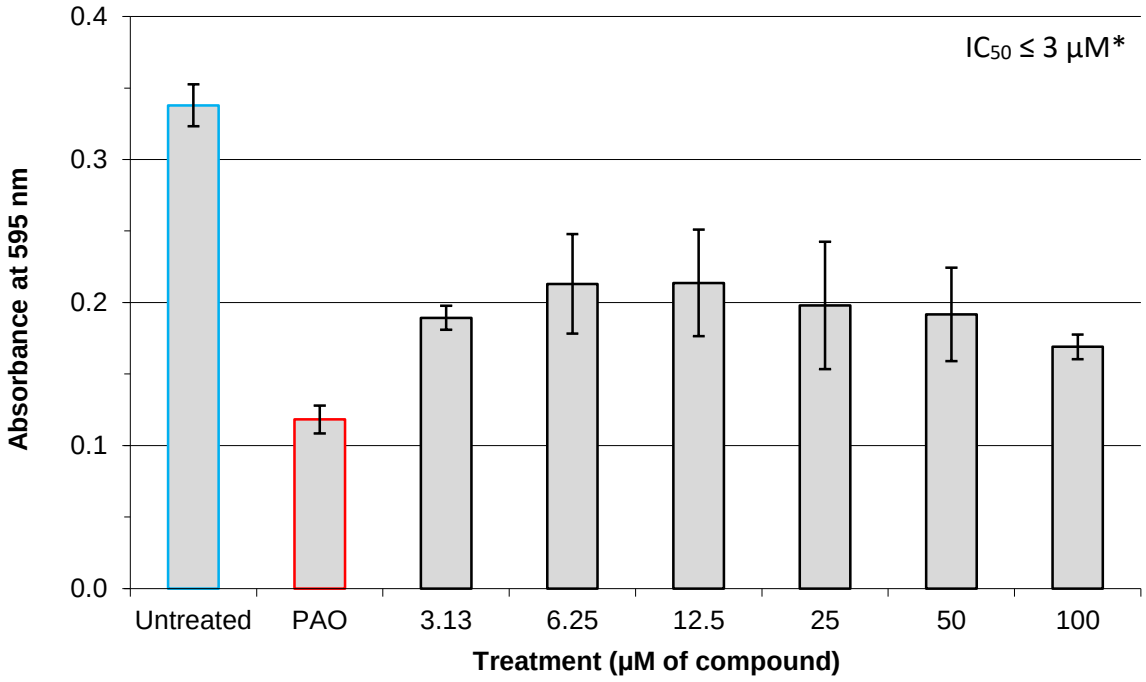


Figure 19 Cytotoxicity of **201ba** towards *mycobacterium abscessus*



** >50% reduction in viability was observed at 3 µM treatment for compound **201cb**, but the absence of data at lower concentrations prevented determination of an accurate IC_{50} value.*
Additionally, further reductions in viability were not observed upon treatment with higher concentrations of the compound

Figure 20 Cytotoxicity of **201cb** towards *mycobacterium abscessus*



** >50% reduction in viability was observed at 3 µM treatment for compound **201bb**, the absence of data at lower concentrations prevented determination of an accurate IC_{50} value. Additionally, further reductions in viability were not observed upon treatment with higher concentrations of the compound*

Figure 21 Cytotoxicity of **201bb** towards *mycobacterium abscessus*

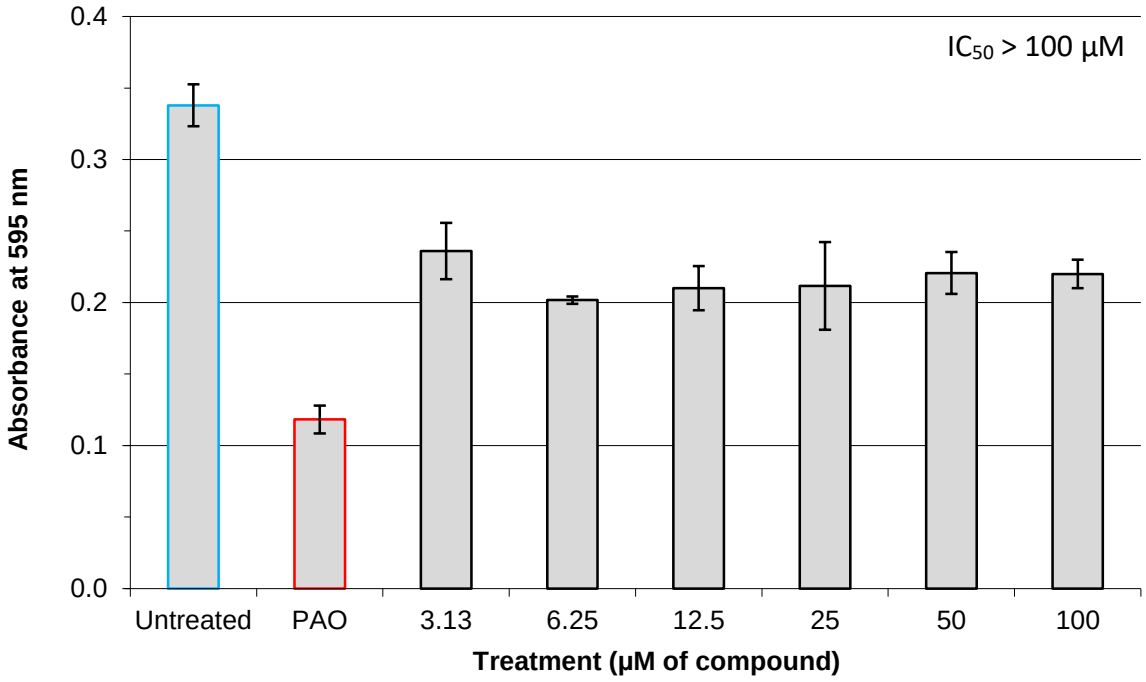


Figure 22 Cytotoxicity of **207a** towards *mycobacterium abscessus*

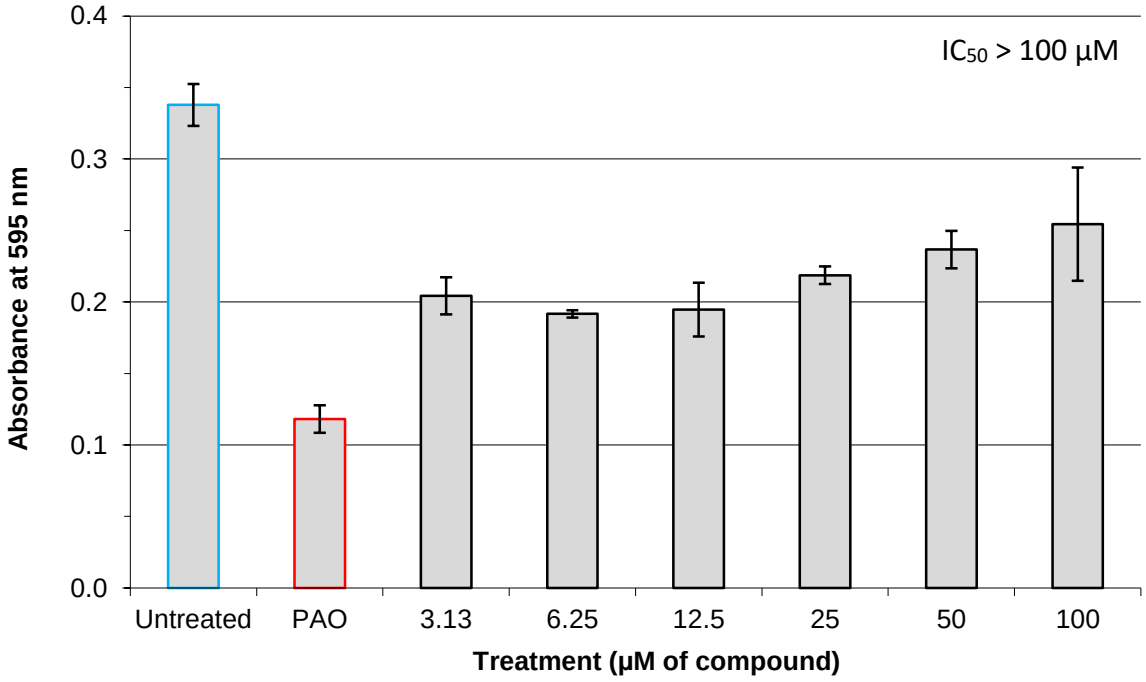


Figure 23 Cytotoxicity of *ent*-**207a** towards *mycobacterium abscessus*

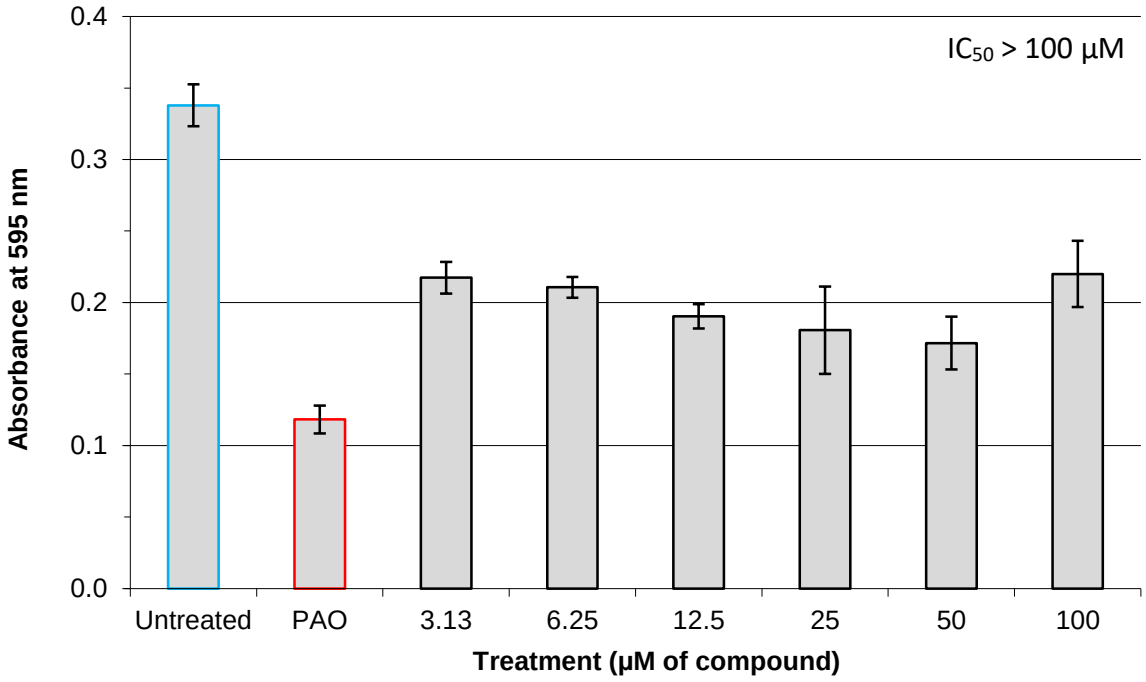


Figure 24 Cytotoxicity of **207d** towards *mycobacterium abscessus*

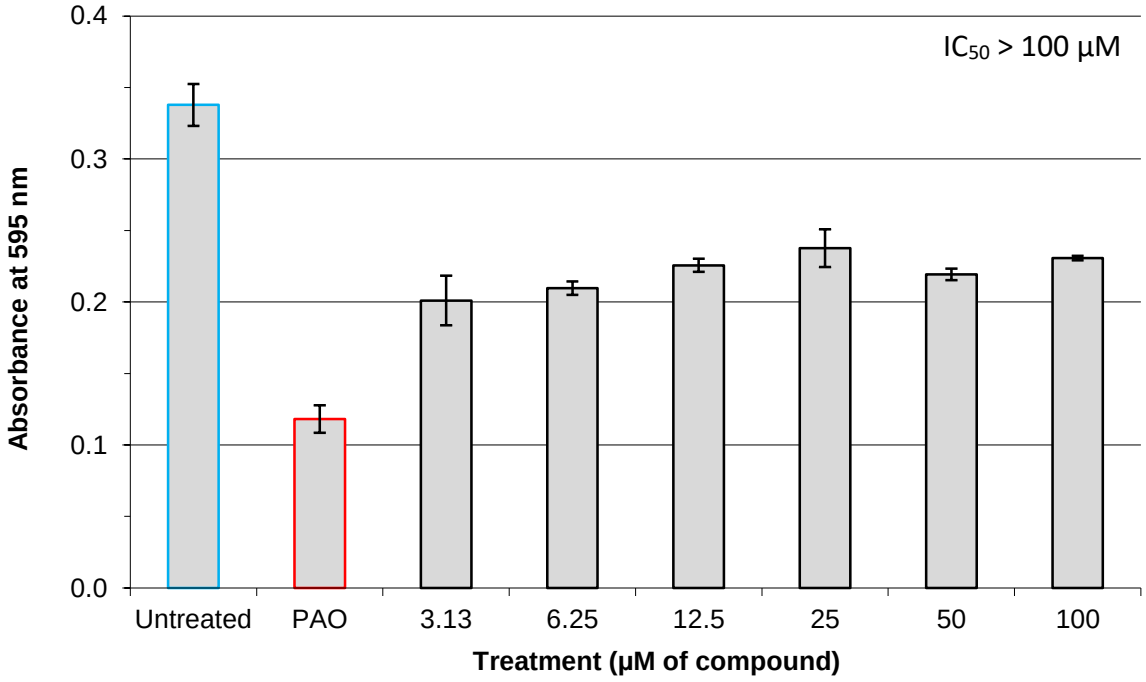


Figure 25 Cytotoxicity of **210a** towards *mycobacterium abscessus*

MTT assay for HeLa (ATCC CCL-2). All compounds were dissolved in DMSO at a concentration of either 100 or 50 mM prior to cell treatment. The cells were treated at concentrations ranging from 0.004 to 100 μM and incubated for 48 h in 200 μL of media. An amount of 20 μL of MTT reagent in serum-free medium (5 mg/mL) was added to each well and incubated further for 2 h. Media was removed, and the resulting formazan crystals were solubilized in 100 μL of DMSO. A490 was measured using a Thermomax Molecular Device plate reader. The experiments were performed in quadruplicate and repeated at least twice for each compound per cell line. Cells treated with 0.1% DMSO were used as a vehicle control, and phenyl arsine oxide (PAO) was used as a positive killing control.

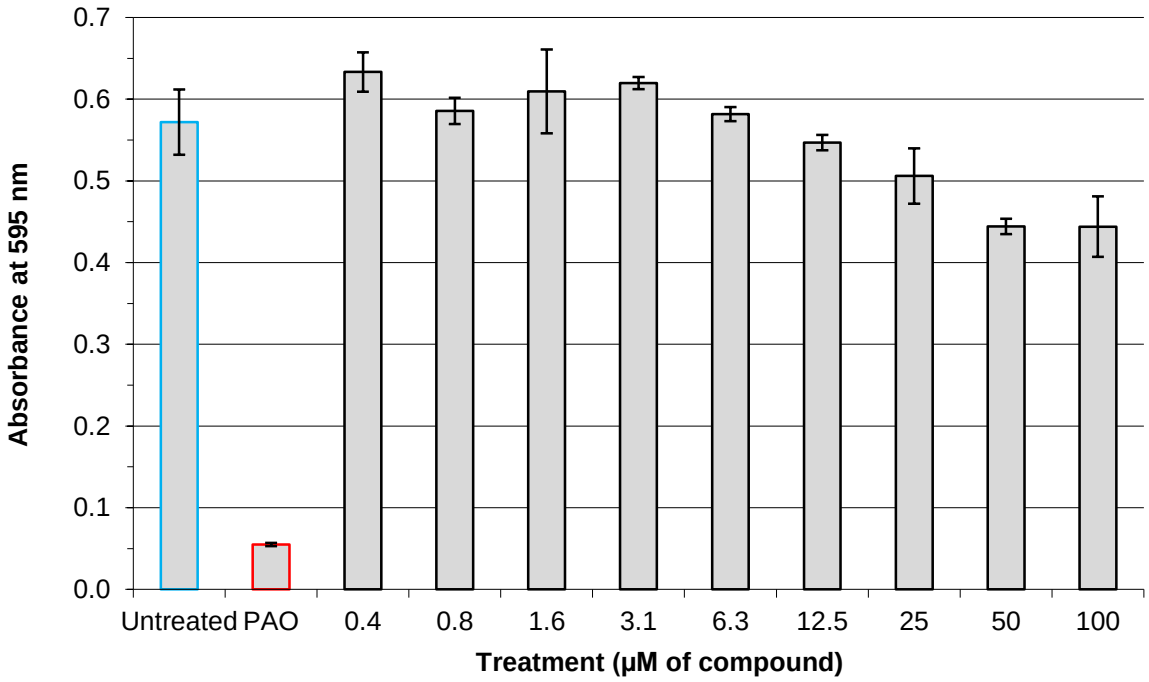


Figure 26 Cytotoxicity of **201aa** towards HeLa cells

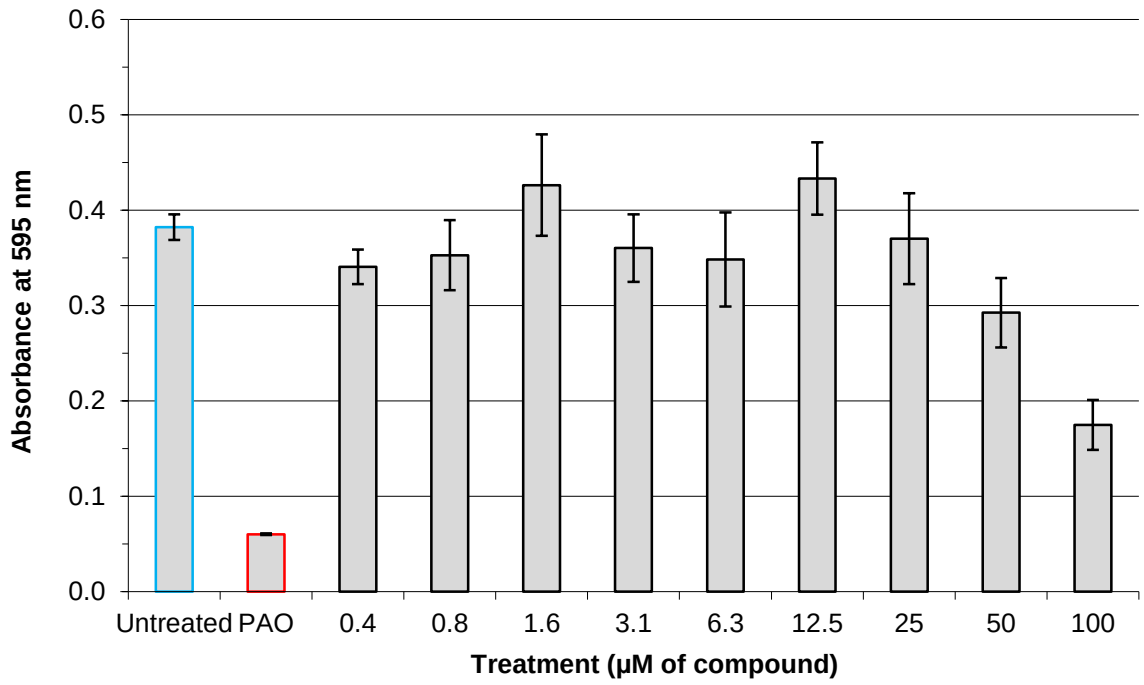


Figure 27 Cytotoxicity of **201ab** towards HeLa cells

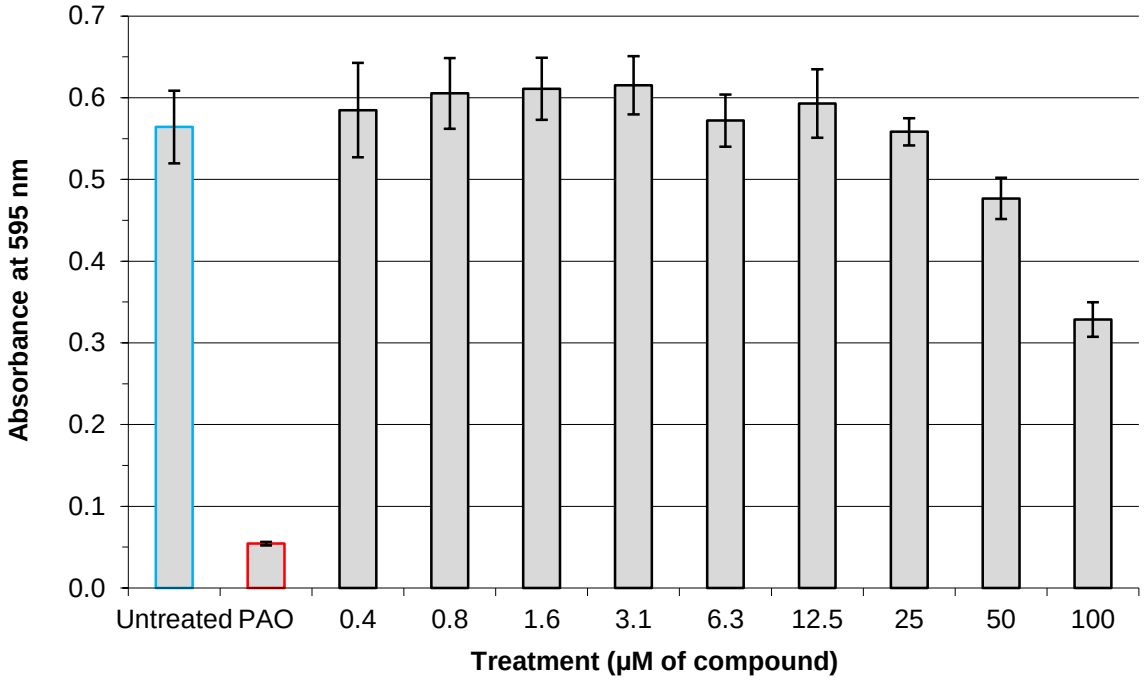


Figure 28 Cytotoxicity of **201ad** towards HeLa cells

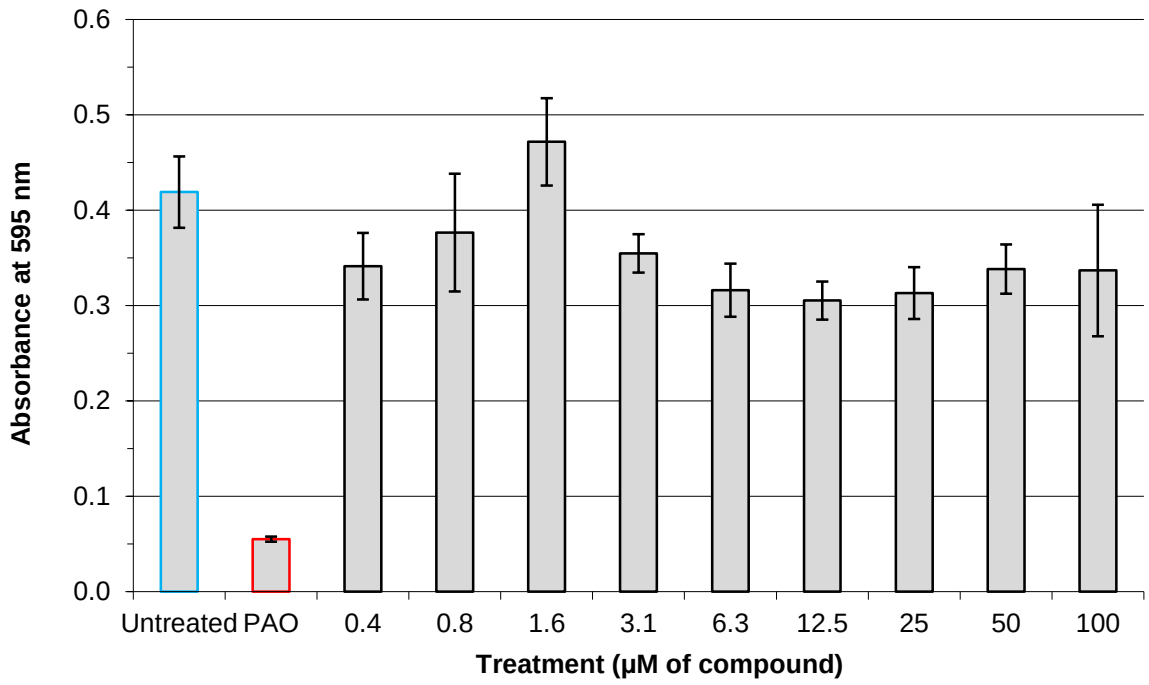


Figure 29 Cytotoxicity of **201ba** towards HeLa cells

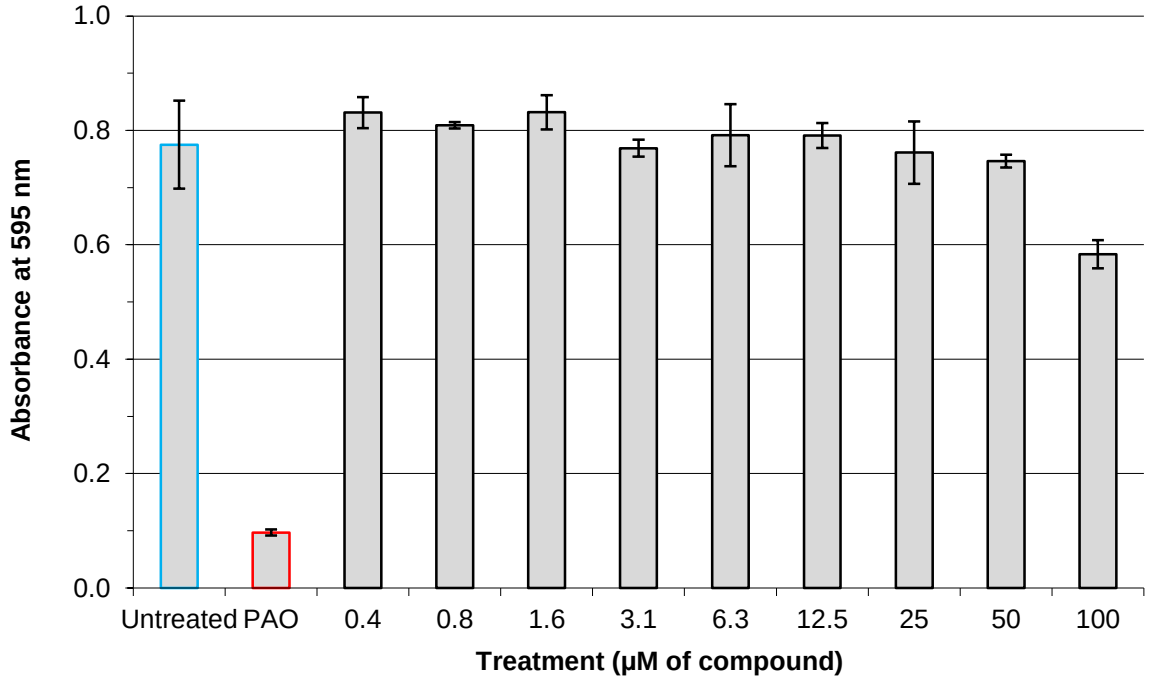


Figure 30 Cytotoxicity of **201cb** towards HeLa cells

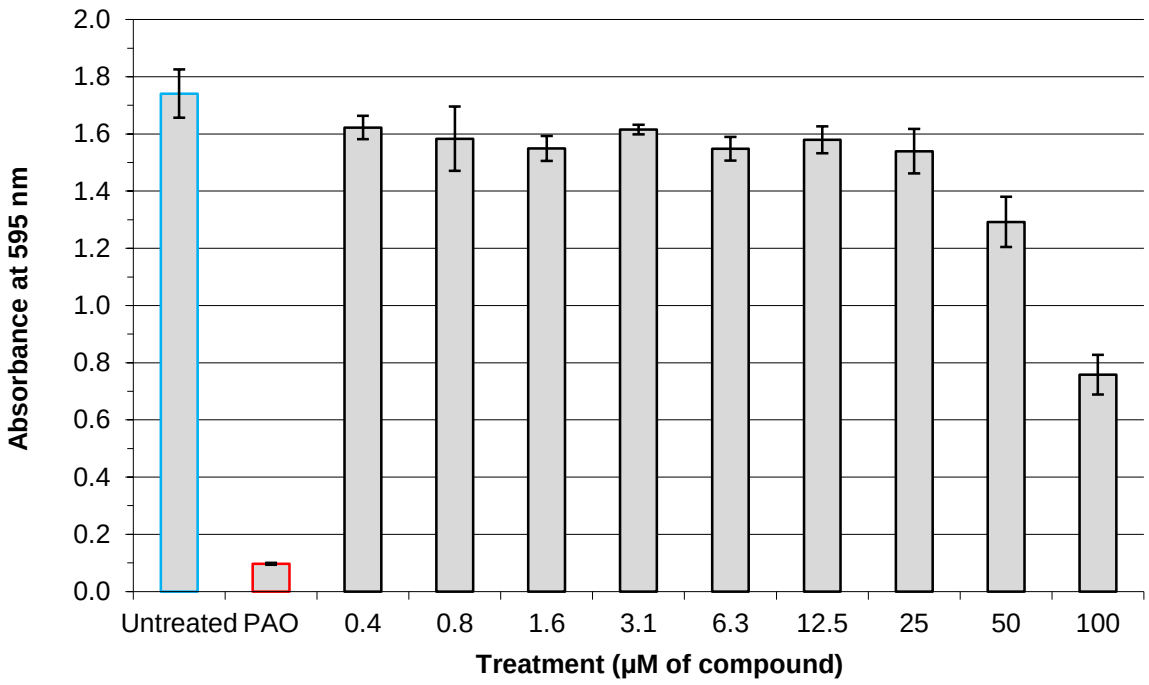


Figure 31 Cytotoxicity of **201bb** towards HeLa cells

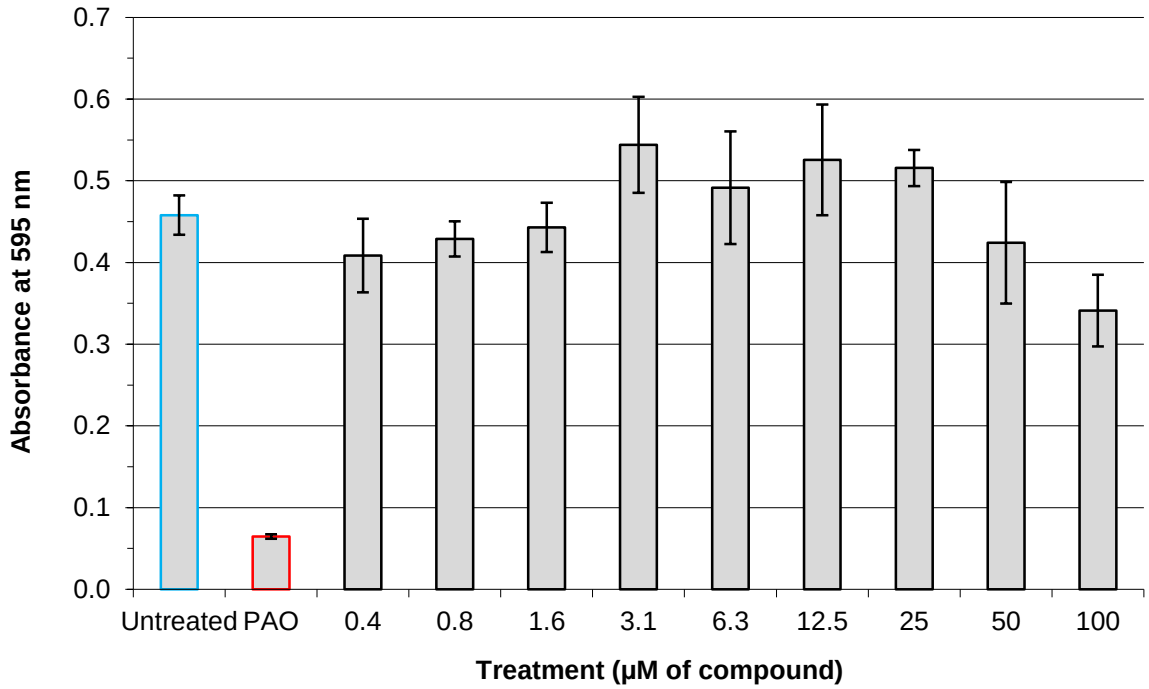


Figure 32 Cytotoxicity of **207a** towards HeLa cells

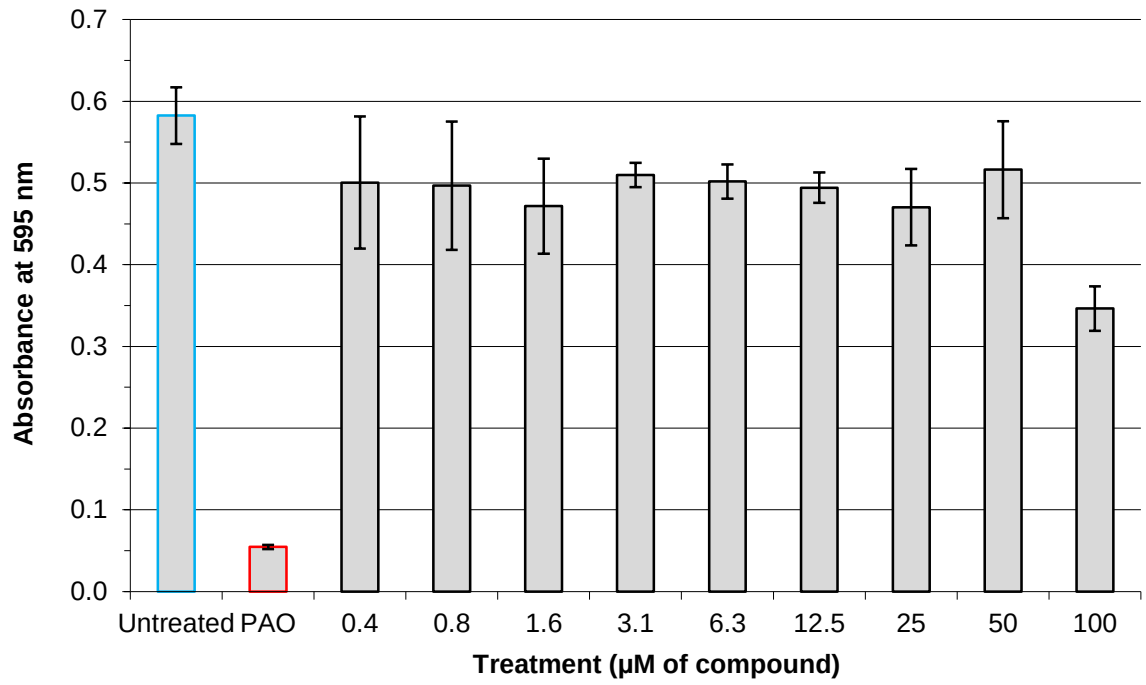


Figure 33 Cytotoxicity of *ent*-**207a** towards HeLa cells

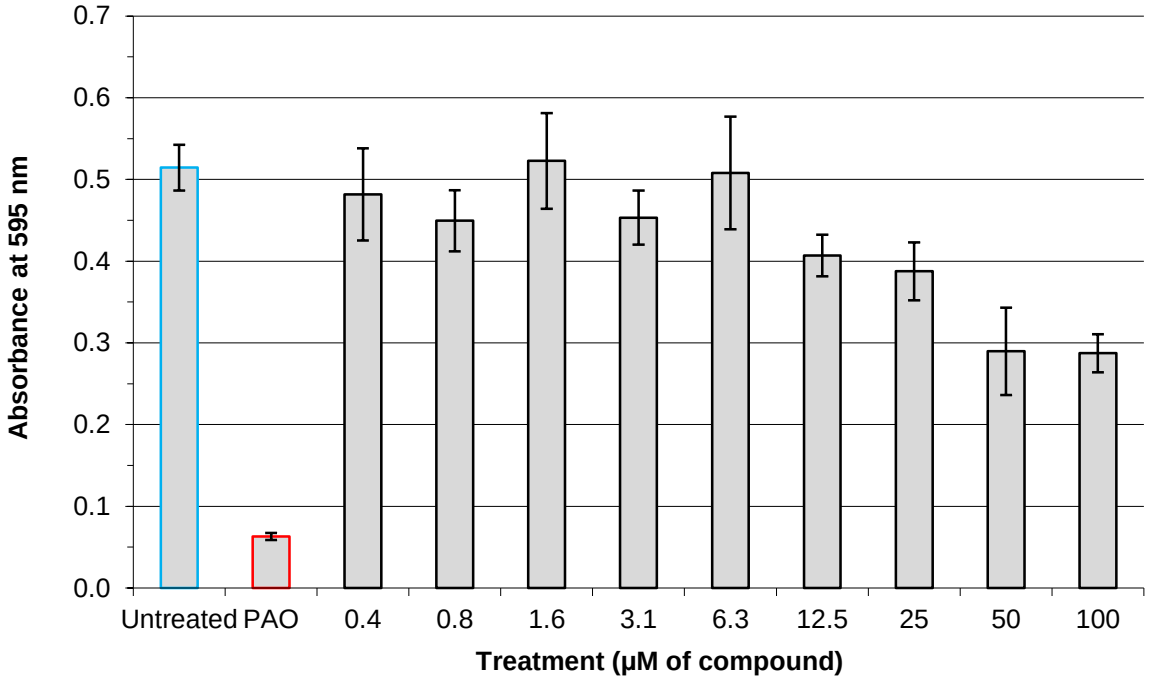


Figure 34 Cytotoxicity of **207d** towards HeLa cells

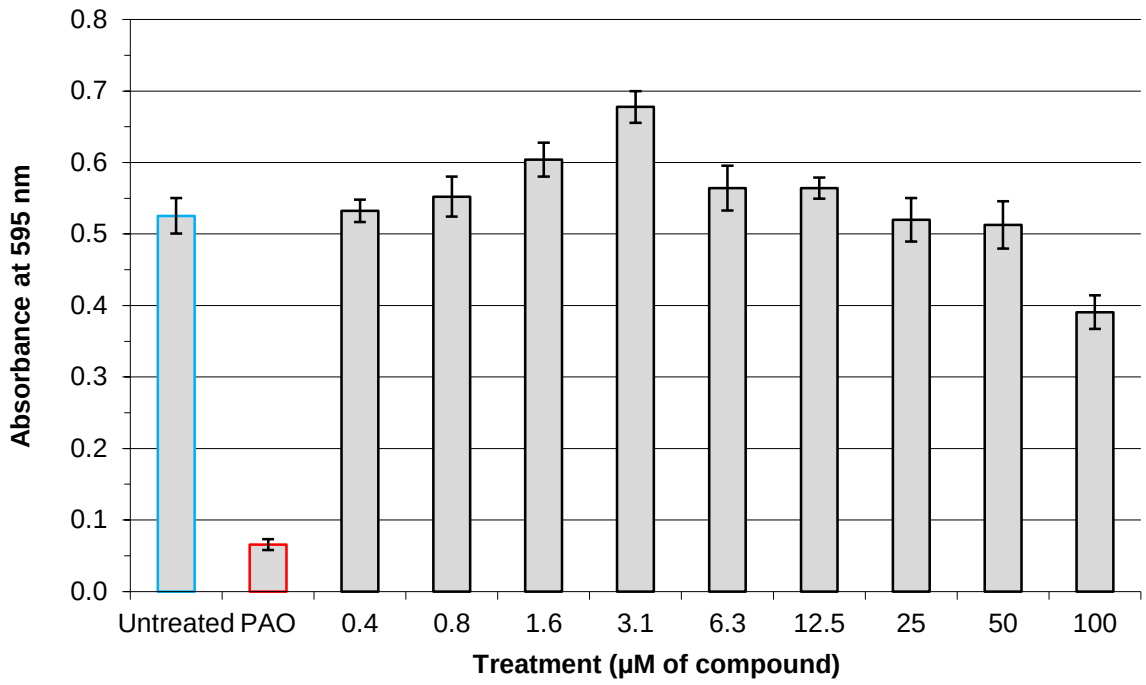


Figure 35 Cytotoxicity of **210a** towards HeLa cells

A2. Evaluation of biological activitie of 2,5-diazabicyclo[5.1.0]octan-6-ones and 2,6-diazabicyclo[6.1.0]nonan-7-ones

The preliminary biological studies were performed by the group of Prof. Frolova (New Mexico Institute of Mining and Technology, Socorro, New Mexico) in the framework of a collaborative project.[4]

To evaluate antiproliferative properties of the synthesized compounds, the cells were trypsinized and seeded $4 \cdot 10^3$ cells per well into 96-well microtiter plates. The cells were grown for 24 h before treatment. MTT assay for HeLa: All compounds were dissolved in DMSO at a concentration of either 100 or 50 mM prior to cell treatment. The cells were treated at concentrations ranging from 0.004 to 100 μM and incubated for 48 h in 200 μL of media. Twenty microliters of MTT reagent in serum-free medium (5 mg/mL) was added to each well and incubated further for 2 h. Media was removed, and the resulting formazan crystals were resolubilized in 100 μL of DMSO. A490 was measured using a Thermomax Molecular Device plate reader. The experiments were performed in quadruplicate and repeated at least twice for each compound per cell line. Cells treated with 0.1% DMSO were used as a negative control, and phenyl arsine oxide (PAO) was used as a positive killing control.

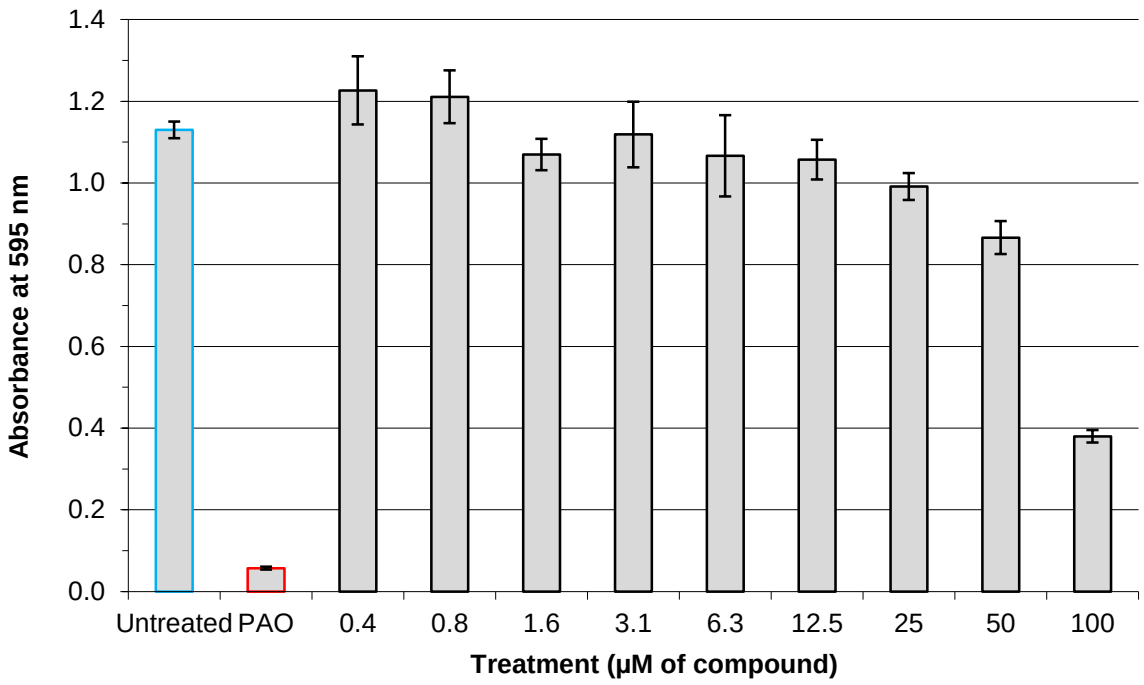


Figure 36 Cytotoxicity of **217ac** towards HeLa cells

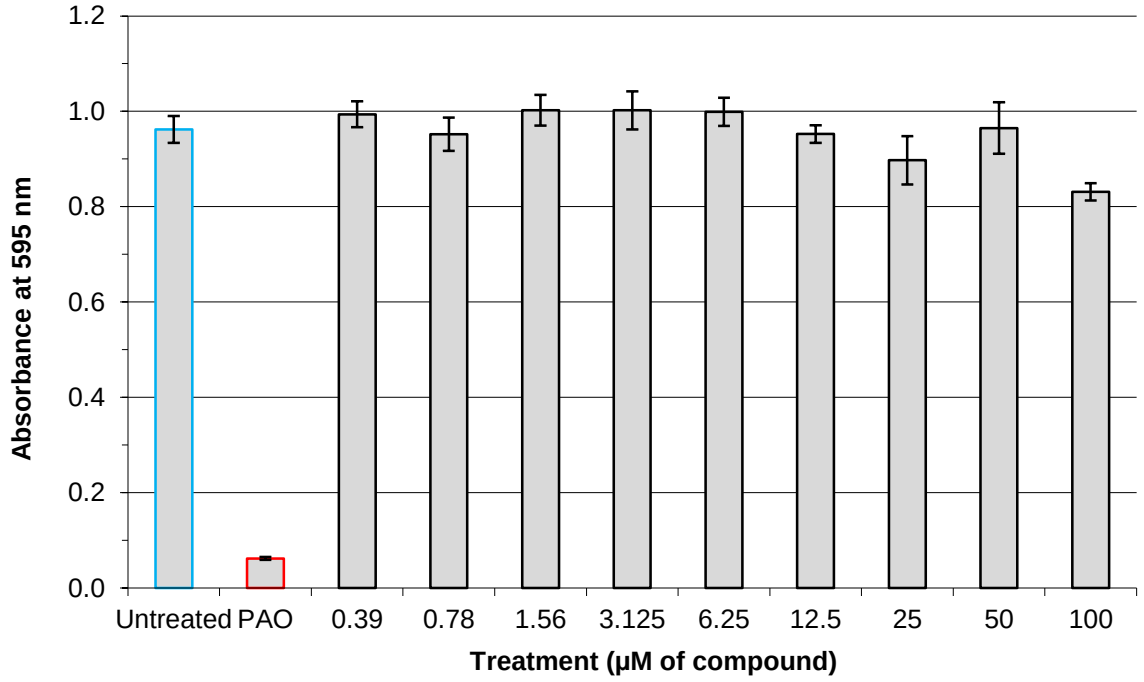


Figure 37 Cytotoxicity of **217ad** towards HeLa cells

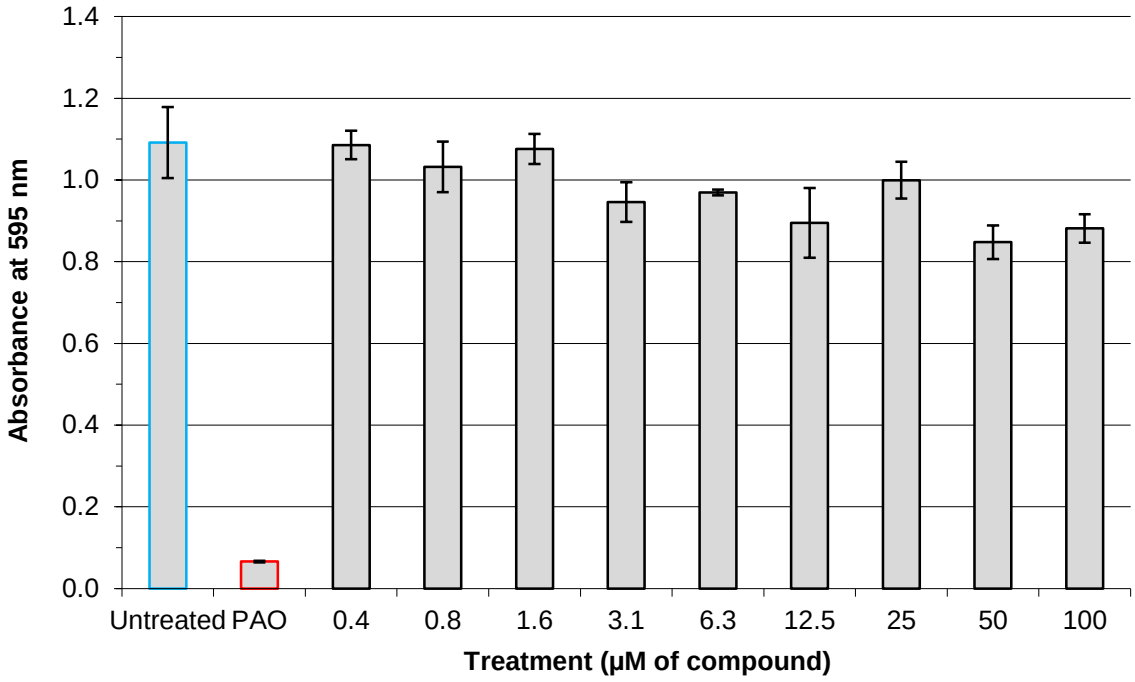


Figure 38 Cytotoxicity of **217ag** towards HeLa cells

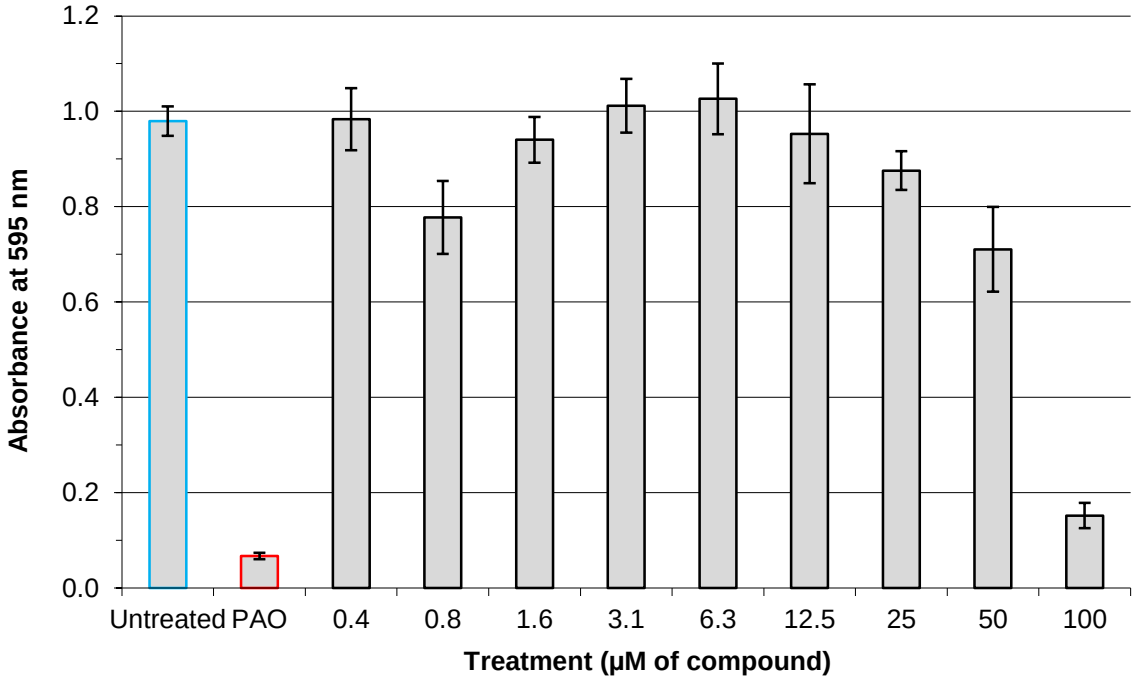


Figure 39 Cytotoxicity of **217ah** towards HeLa cells

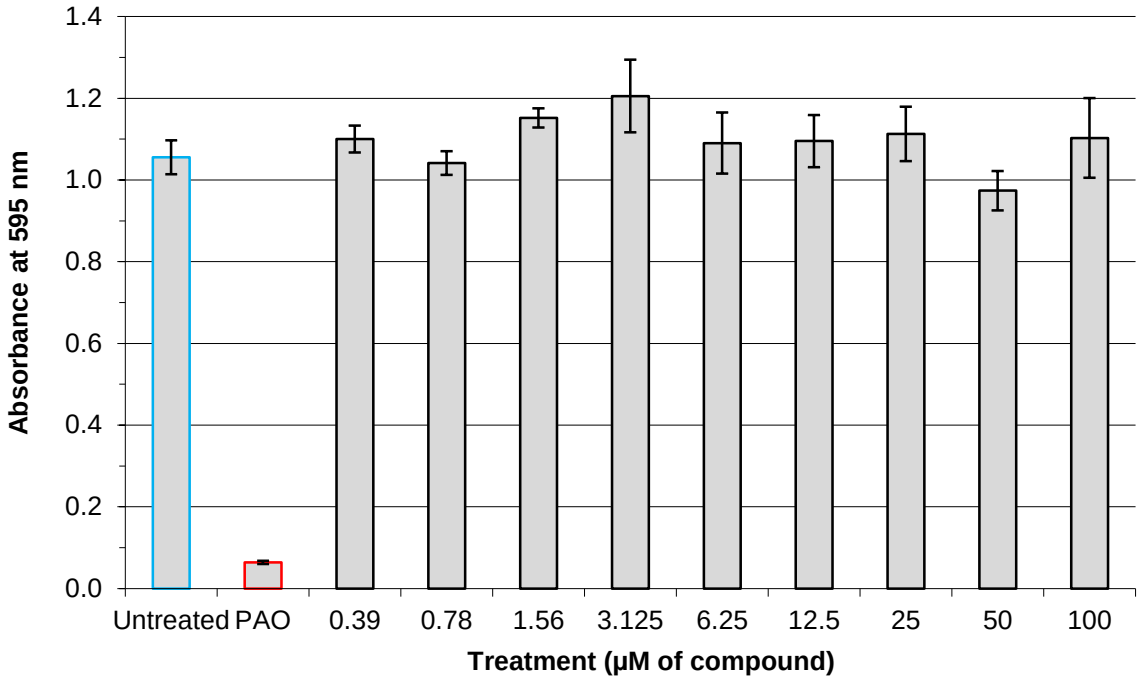


Figure 40 Cytotoxicity of **217be** towards HeLa cells

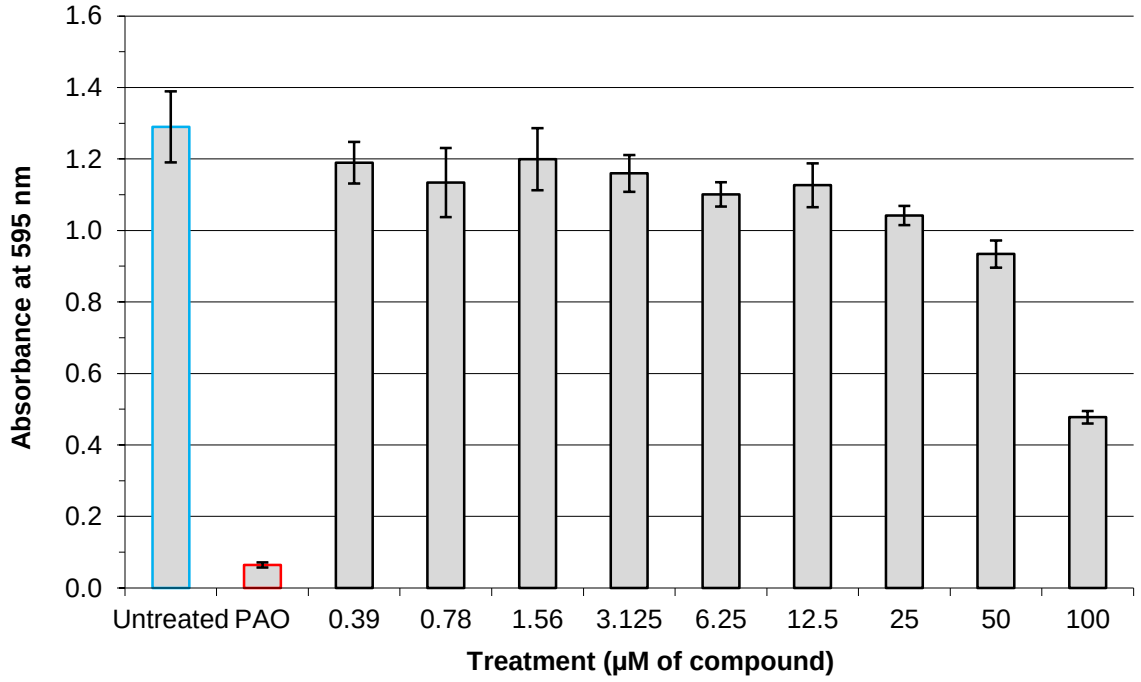


Figure 41 Cytotoxicity of **217ch** towards HeLa cells

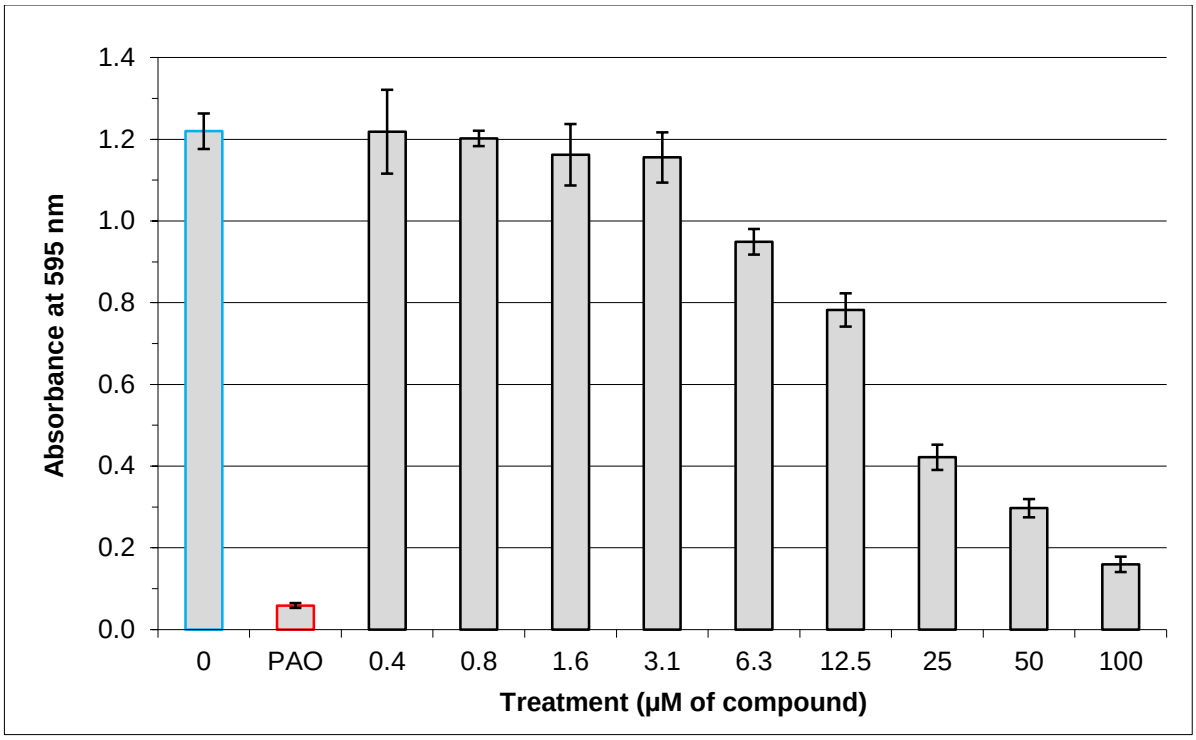


Figure 42 Cytotoxicity of **217gc** towards HeLa cells

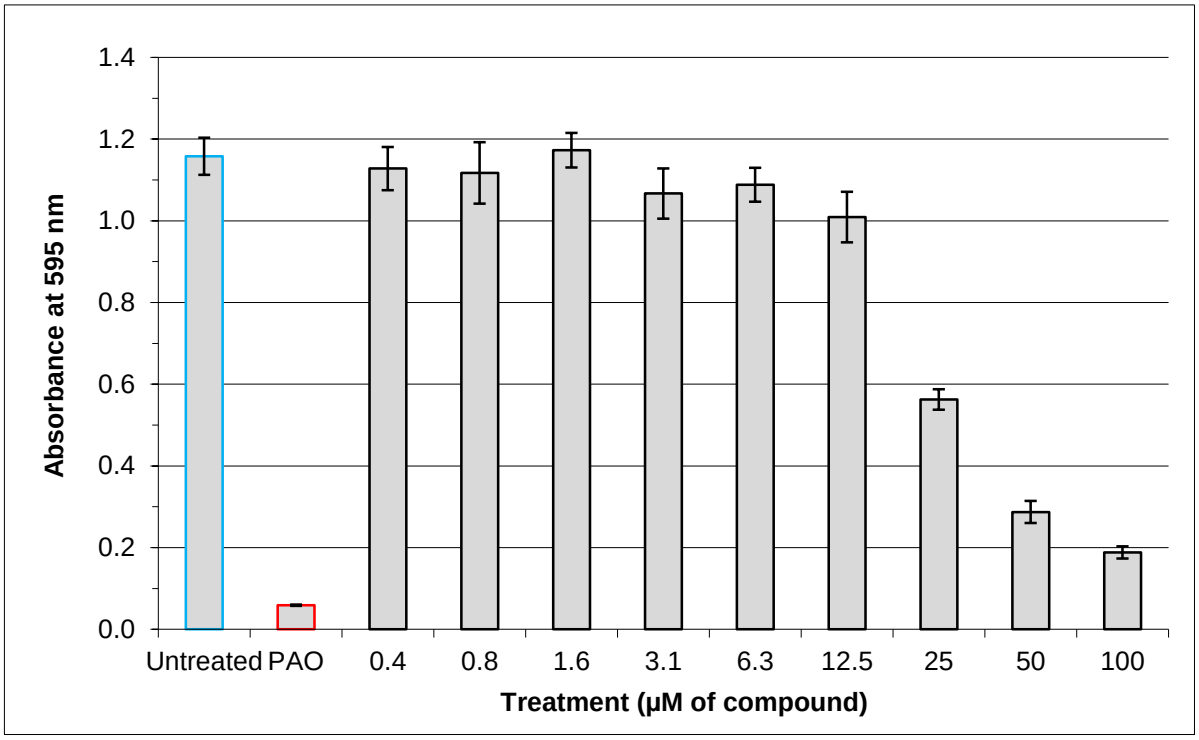


Figure 43 Cytotoxicity of **217gj** towards HeLa cells

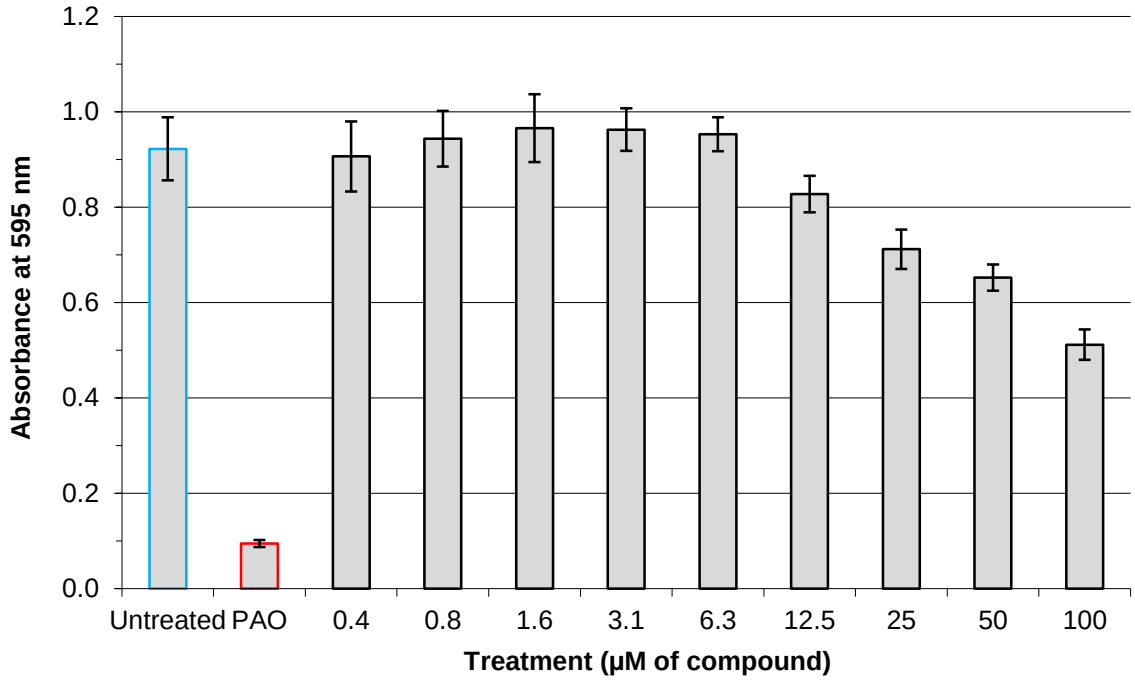


Figure 44 Cytotoxicity of **217ha** towards HeLa cells

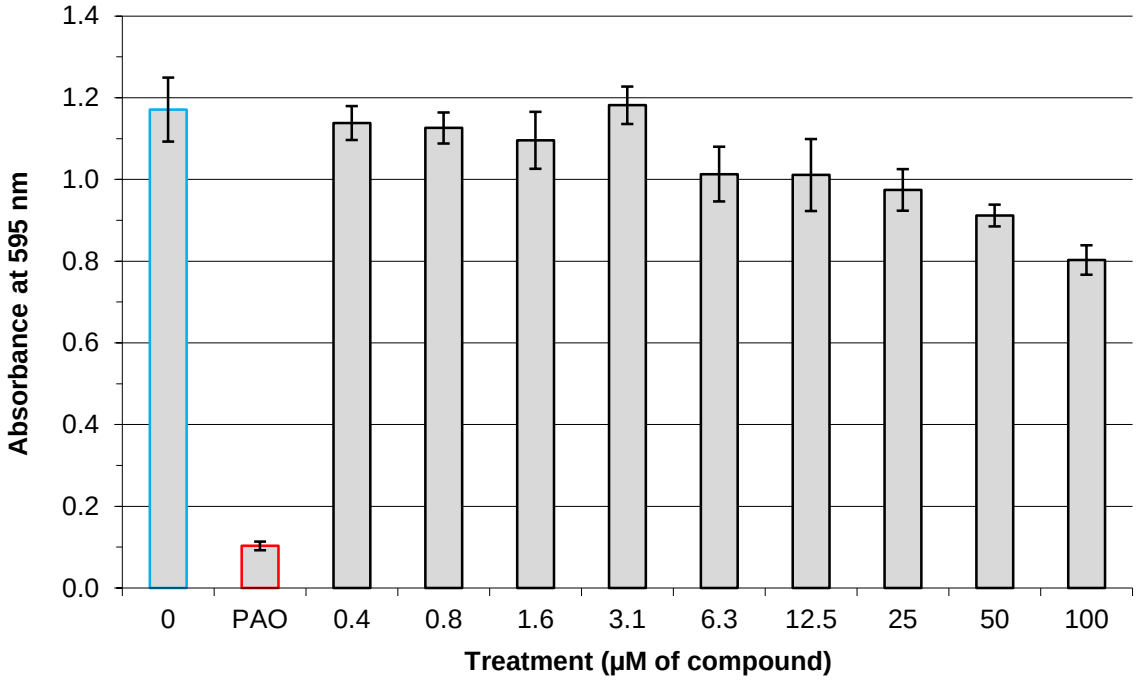


Figure 45 Cytotoxicity of **217hh** towards HeLa cells

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